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(54) **Intranasal calcitonin formulations.**

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EP-A- 0 277 462
EP-A- 0 363 876
GB-A- 2 213 377

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Description

The present invention relates to a novel intranasal composition, a method for enhancing the bioavailability of a polypeptide having calcitonin activity and the use of $^{\Delta}$-aminolevulinic acid to prepare an intranasal composition.

The method of administration of pharmaceutically active calcitonin is predominantly by injection, although efforts were made in the prior art to use other modes of administration. While administration by injection is acceptable for short-term therapy, administration by injection to patients in need of long-term calcitonin therapy has serious problems. Not only is it costly to patients to have physicians do the administration for extended periods of time, but it is also painful and inconvenient. Nor can calcitonin be given orally to patients since oral administration will result in degradation of calcitonin.

Recently, the prior art has found that calcitonin may also be administered via intranasal route and proposed various compositions for such administration. In general, calcitonin is in admixture with a pharmaceutically acceptable vehicle which may comprise an aqueous base, an oil-in-water or water-in-oil emulsion or an oily solvent base suitable for use on the mucous membranes, such as mineral or vegetable oils and fatty acid esters and one or more chemicals which are soluble in the base. While small molecular weight polypeptides, such as tripeptides and tetrapeptides, are efficiently absorbed intranasally, larger molecules, such as calcitonin, have been found to require the presence of absorption promoters to enhance absorption across mucous membranes. To that end, absorption promoters, such as chelating agents, surface active agents and the like are used in intranasal formulations. Notwithstanding their beneficial effects, some absorption promoters found to exhibit the undesirable property of producing irritation on the nasal membrane.

More recently, it has also been found that systemic bioavailability of calcitonin is limited not only by absorption factors but the extent of degradation of calcitonin into pharmacologically inactive fragments by the action of nasal mucosal peptidases.

As a result of extensive investigations of various formulations of calcitonin for intranasal administration, the present inventors have found that nasal mucosal peptidases may be inhibited by the use of $^{\Delta}$-aminolevulinic acid, when co-administered intranasally with calcitonin. Such co-administration may be accomplished using various pharmaceutically acceptable formulations suitable for nasal application.

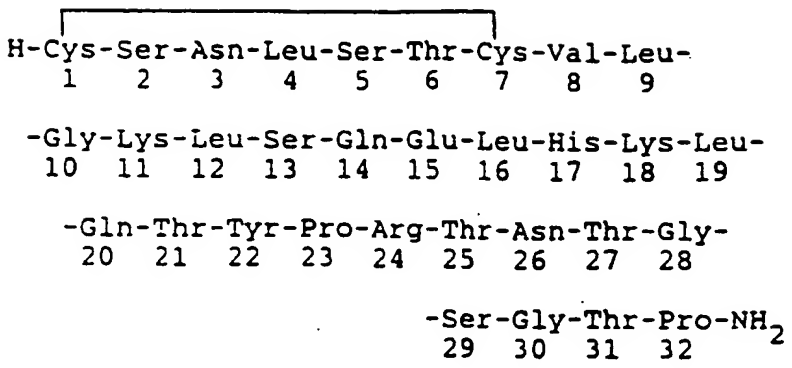
This invention relates to an intranasal formulation comprising: from 0001% w/v to 15% w/v of calcitonin as hereinafter defined; from 0.0005% w/v to 10% w/v of $^{\Delta}$-aminolevulinic acid; and a pharmaceutically acceptable vehicle. The invention also relates to a method for increasing the bioavailability of calcitonin by inhibiting nasal mucosal peptidases utilizing $^{\Delta}$-aminolevulinic acid in the intranasal formulations.

The present invention also relates to the use of $^{\Delta}$-aminolevulinic acid to prepare an intranasal composition as defined above for treating hyperparathyroidism, idiopathic hypercalcemia of infancy, Paget's disease, vitamin D intoxication, or osteolytic bone metastases said diseases being characterized by hypercalcemia and high phosphate concentrations in the blood. Their treatment is effected by decreasing serum calcium and phosphate concentrations in the blood by intranasal application of a calcitonin containing composition to effect control of said diseases by transephitelial action.

The term calcitonin as used herein means not only polypeptides having a structure corresponding to one of the naturally occurring hormones, and which may be naturally or synthetically produced, but also analogs thereof and related synthetic peptides having calcitonin activity.

In accordance with the present invention, intranasal pharmaceutical formulations are provided in which the peptidase-inhibiting agent, $^{\Delta}$-aminolevulinic acid, is incorporated for enhancing the bioavailability of calcitonin. The composition of the formulations are described hereunder.

Calcitonin is a polypeptide hormone involved in the control of calcium metabolism in the body. All known natural calcitonin peptides contain an amino acid sequence of 32 amino acids, of which the seven at the amino terminal end of the peptide chain are held in a cyclic configuration by a sulphur or carbon bridge and the carboxyl terminal residue consists of proline amide. The natural calcitonins include the salmon, eel, bovin, procine, ovine, rat and human calcitonins. The detailed structure within the peptide chain of the hormone varies among different species and while the hormones, and their derivatives and analogues found in various species are of interest for use in the present invention, salmon calcitonin is of special interest in view of its relatively hydrophobic character and its stability. Salmon calcitonin has the following formula:



In U.S. Patent Nos. 3,926,938, 4,062,815, 3,929,758, 4,033,940, 4,336,187, 4,388,235, 4,391,747 and 4,401,593 are disclosed improved synthesis of calcitonins including the salmon calcitonin referred to above.

Human, salmon and procine calcitonins have been available for therapeutic use for several years. For example, synthetic salmon calcitonin is marketed by Armour Pharmaceutical Co. under the tradename CALCIMAR in a sterile, lyophilized form reconstitutable for subcutaneous or intravascular injection for the treatment of bone diseases.

The level of hypocalcemic activity of calcitonins varies from species to species. Salmon and chicken calcitonin have a potency of about 4,000 to 6,000 MCR (Medical Research Council) U/mg peptide; eel calcitonin about 2,000 to 4,000 MRC U/mg peptide; rat 400 MRC U/mg; while beef, sheep, hog and man about 100 to 200 MRC U/mg peptide.

Calcitonin used by the present invention may be obtained from Armour Pharmaceutical Co., from natural sources, or by synthetic routes known in the art. The synthesis can be performed by classical peptide synthesis as well as by solid phase synthesis.

In addition to the above-described calcitonins, the present invention encompasses synthetic calcitonin peptides having biological activity of the same type as those above-described. Such synthetic calcitonins are disclosed, along with processes for preparation thereof in the following U.S. Patent Nos.

4,388,235	4,604,238
4,391,747	4,605,514
4,397,780	4,605,515
4,401,593	4,606,856
4,414,149	4,622,386
4,444,681	4,622,387
4,451,395	4,622,388
4,469,636	4,632,978
4,497,731	4,639,509
4,497,732	4,639,510
4,528,132	4,639,511
4,537,716	4,650,854
4,597,900	4,659,804
4,604,236	4,732,969
4,604,237	4,746,728

Synthetic calcitonin analogues disclosed in these patents are incorporated herein by reference as if set out in full herein. This list is representative of the analogues useful in the present invention.

In accordance for the foregoing, the following analogues of calcitonin constitute specific active ingredients used in the various intranasal formulations of the present invention:

1. Des Asparagine-3-Calcitonins having the structures:

(a)

H-Cys-Ser-Leu-Ser-Thr-Cys-Val-Leu-Gly-Lys-Leu-
Ser-Gln-Glu-Leu-His-Lys-Leu-Gln-Thr-Tyr-Pro-
Arg-Thr-Asn-Thr-Gly-Ser-Gly-Thr-Pro-NH_2;

(b)

Cys-Ser-Leu-Ser-Thr-Cys-Val-Leu-Gly-Lys-Leu-Ser-
Gln-Glu-Leu-His-Lys-Leu-Gln-Thr-Tyr-Pro-Arg-Thr-
Asp-Val-Gly-Ala-Gly-Thr-Pro-NH_2.

2. [16-Alanine] Calcitonins having the following structures:

(a)

Cys-Ser-Asn-Leu-Ser-Thr-Cys-Val-Leu-Gly-
-Lys-Leu-Ser-Gln-Glu-Ala-His-Lys-Leu-Gln-
-Thr-Tyr-Pro-Arg-Thr-Asn-Thr-Gly-Ser-Gly-
-Thr-Pro-NH_2 (Salmon);

(b)

Cys-Ser-Asn-Leu-Ser-Thr-Cys-Val-Leu-Gly-
-Lys-Leu-Ser-Gln-Glu-Ala-His-Lys-Leu-Gln-
-Thr-Tyr-Pro-Arg-Thr-Asp-Val-Gly-Ala-Gly-
-Thr-Pro-NH_2 (Eel); and

(c)

Cys-Gly-Asn-Leu-Ser-Thr-Cys-Met-Leu-Gly-
-Thr-Tyr-Thr-Gln-Asp-Ala-Asn-Lys-Phe-His-
-Thr-Phe-Pro-Gln-Thr-Ala-Ile-Gly-Val-Gly-
-Ala-Pro-NH_2 (Human).

3. Des ^{2}-Glycine ^{8}-Des ^{22}-Calcitonins having the structures:

(a)

H-Cys-Asn-Leu-Ser-Thr-Cys-Gly-Leu-
-Gly-Lys-Leu-Ser-Gln-Glu-Leu-His-
-Lys-Leu-Gln-Thr-Pro-Arg-Thr-Asn-
-Thr-Gly-Ser-Gly-Thr-Pro-NH_2 (Salmon); and

(b)

H-Cys-Asn-Leu-Ser-Thr-Cys-Gly-Leu-
-Gly-Lys-Leu-Ser-Gln-Glu-Leu-His-
-Lys-Leu-Gln-Thr-Pro-Arg-Thr-Asp-
-Val-Gly-Ala-Gly-Thr-Pro-Nh_2 (Eel).

4. Des-13-Calcitonins having the following structures:

(a)

Cys-Ser-Asn-Leu-Ser-Thr-Cys-Val-Leu-Gly-
-Lys-Leu-Gln-Glu-Leu-His-Lys-
-Leu-Gln-Thr-Tyr-Pro-Arg-Thr-Asn-
-Thr-Gly-Ser-Gly-Thr-Pro-NH_2;

(b)

Cys-Ser-Asn-Leu-Ser-Thr-Cys-Val-Leu-Gly-
-Lys-Leu-Gln-Glu-Leu-His-Lys-Leu-Gln-
-Thr-Tyr-Pro-Arg-Thr-Asp-Val-Gly-Ala-
-Gly-Thr-Pro-NH_2; and

(c)

Cys-Gly-Asn-Leu-Ser-Thr-Cys-Met-Leu-Gly-
-Thr-Tyr-Gln-Asp-Phe-Asn-Lys-Phe-His-
-The-Phe-Pro-Gln-Thr-Ala-Ile-Gly-Val-
-Gly-Ala-Pro-NH_2.

5. Des-21-Threonine-Calcitonins having the following structures:

(a)

Cys-Ser-Asn-Leu-Ser-Thr-Cys-Val-Leu-Gly-
-Lys-Leu-Ser-Gln-Glu-Leu-His-Lys-Leu-Gln-
-Tyr-Pro-Arg-Thr-Asn-Thr-Gly-Ser-Gly-Thr-
-Pro-NH_2 (Salmon);

(b)

Cys-Ser-Asn-Leu-Ser-Thr-Cys-Val-Leu-Gly-
-Lys-Leu-Ser-Gln-Glu-Leu-His-Lys-Leu-Gln-
-Tyr-Pro-Arg-Thr-Asp-Val-Gly-Ala-Gly-Thr-
-Pro-NH_2, (Eel); and

(c)

Cys-Gly-Asn-Leu-Ser-Thr-Cys-Met-Leu-Gly-
-Thr-Tyr-Thr-Gln-Asp-Phe-Asn-Lys-Phe-His-
-Phe-Pro-Gln-Thr-Ala-Ile-Gly-Val-Gly-Ala-
-Pro-NH_2 (Human).

6. [Gly^2, Ser^3, Gly^8, des-Tyr^{22}] Calcitonins having the following structures:

(a)

Cys-Gly-Ser-Leu-Ser-Thr-Cys-Gly-Leu-Gly-
-Lys-Leu-Ser-Gln-Glu-Leu-His-
-Lys-Leu-Gln-Thr-Pro-Arg-Thr-Asn-
-Thr-Gly-Ser-Gly-Thr-Pro-NH_2; and

(b)

Cys-Gly-Ser-Leu-Ser-Thr-Cys-Gly-Lue-Gly-
-Lys-Leu-Ser-Gln-Glu-Leu-His-
-Lys-Leu-Gln-Thr-Pro-Arg-Thr-Asp-
-Val-Gly-Ala-Gly-Thr-Pro-NH_2.

7. Des-4-Leucine-Calcitonins having the following structures:

(a) Cys-Ser-Asn-Ser-Thr-Cys-Val-Leu-Gly-Lys-Leu-
-Ser-Gln-Glu-Leu-His-Lys-Leu-Gln-Thr-Tyr-
-Pro-Arg-Thr-Asn-Thr-Gly-Ser-Gly-Thr-Pro-
$-NH_2$ (Salmon);

(b) Cys-Ser-Asn-Ser-Thr-Cys-Val-Leu-Gly-Lys-Leu-
-Ser-Gln-Glu-Leu-His-Lys-Leu-Gln-Thr-Tyr-
-Pro-Arg-Thr-Asp-Val-Gly-Ala-Gly-Thr-Pro-
$-NH_2$ (Eel); and

(c) Cys-Gly-Asn-Ser-Thr-Cys-Met-Leu-Gly-Thr-Tyr-
-Thr-Gln-Asp-Phe-Asn-Lys-Phe-His-Thr-Phe-
-Pro-Gln-Thr-Ala-Ile-Gly-Val-Gly-Ala-Pro-
$-NH_2$ (Human).

8. Calcitonin-(1-23)-Peptide Amides having the following structures:

(a)

Cys-Ser-Asn-Leu-Ser-Thr-Cys-Val-Leu-Gly-
-Lys-Leu-Ser-Gln-Glu-Leu-His-Lys-Leu-
-Gln-Thr-Tyr-Pro-NH_2; and

(b)

R_1 R_2
Cys-Ser-Asn-Leu-Ser-Thr-Cys-Val-Leu-Gly-
Lys-Leu-Ser-Gln-Glu-Leu-His-Lys-Leu-Gln-
-Thr-Tyr-Pro-NH_2.

where R_1 is S-n-alkyl, Cys or H and R_2 is S-n-alkyl or H, R_1 being S-n-alkyl, Cys or H when R_2 is H and R_2 being s-n-alkyl or H when R_1 is H.

9. [Des-1-Amino,8-Glycine) Calcitonins having the following structures:

(a)

Bmp-Ser-Asn-Leu-Ser-Thr-Cys-Gly-Leu-Gly-
Lys-Leu-Ser-Gln-Glu-Leu-His-Lys-Leu-Gln-
Thr-Tyr-Pro-Arg-Thr-Asn-Thr-Gly-Ser-Gly-
-Thr-Pro-NH_2 (Salmon); and

(b)

Bmp-Ser-Asn-Leu-Ser-Thr-Cys-Val-Leu-Gly-
Lys-Leu-Ser-Gln-Glu-Leu-His-Lys-Leu-Gln-
Thr-Tyr-Pro-Arg-Thr-Asp-Val-Gly-Ala-Gly-
-Thr-Pro-NH_2 (Eel).

10. [1,7-Di-Alanine] Calcitonins having the following structures:

(a)

Ala-Ser-Asn-Leu-Ser-Thr-Ala-Val-Leu-Gly-Lys-
Leu-Ser-Gln-Glu-Ala-His-Lys-Leu-Gln-Thr-Tyr-
Pro-Arg-Thr-Asn-Thr-Gly-Ser-Gly-Thr-Pro-NH_2;

(b) Ala-Ser-Asn-Leu-Ser-Thr-Ala-Val-Leu-Gly-Lys-
Leu-Ser-Gln-Glu-Ala-His-Lys-Leu-Gln-Thr-
Tyr-Pro-Arg-Thr-Asp-Val-Gly-Ala-
-Gly-Thr-Pro-NH_2.

11. 8-Methionine Calcitonins having the following structures:

(a)

Cys-Ser-Asn-Leu-Ser-Thr-Cys-Met-Leu-
Gly-Lys-Leu-Ser-Gln-Glu-Leu-His-Lys-
Leu-Gln-Thr-Tyr-Pro-Arg-Thr-Asn-Thr-
Gly-Ser-Gly-Thr-Pro-NH_2; and

(b)

Cys-Ser-Asn-Leu-Ser-Thr-Cys-Met-Leu-
Gly-Lys-Leu-Ser-Gln-Glu-Leu-His-Lys-
Leu-Gln-Thr-Tyr-Pro-Arg-Thr-Asp-Val-
Gly-Ala-Gly-Thr-Pro-NH_2.

12. Des-2-Serine, 3-Asparagine Calcitonins having the following structures:

(a)

Cys-Leu-Ser-Thr-Cys-Val-Leu-Gly-Lys-
Leu-Ser-Gln-Glu-Leu-His-Lys-Leu-Gln-
Thr-Tyr-Pro-Arg-Thr-Asn-Thr-Gly-Ser-
Gly-Thr-Pro-NH_2; and

(b)

Cys-Leu-Ser-Thr-Cys-Val-Leu-Gly-Lys-
Leu-Scr-Gln-Glu-Leu-His-Lys-Leu-Gln-
Thr-Tyr-Pro-Arg-Thr-Asp-Val-Gly-Ala-
Gly-Thr-Pro-NH_2.

13. G-Serine, Des-19-Leucine Calcitonins having the following structures:

(a)

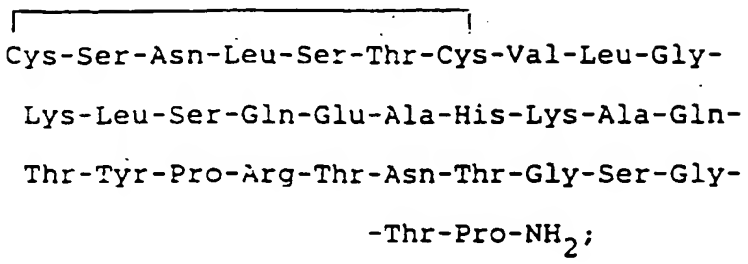
Cys-Ser-Asn-Leu-Ser-Ser-Cys-Val-Leu-Gly-
Lys-Leu-Ser-Gln-Glu-Leu-His-Lys-Gln-Thr-
Tyr-Pro-Arg-Thr-Asn-Thr-Gly-Ser-
-Gly-Thr-Pro-NH_2; and

(b)

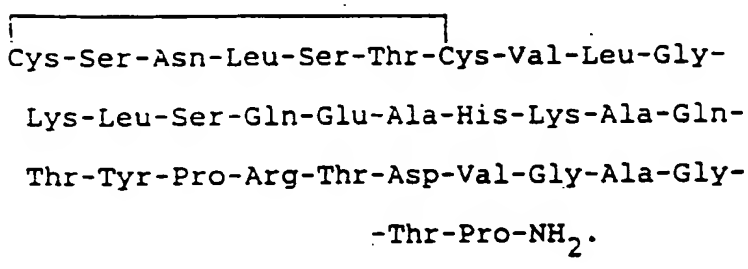
Cys-Ser-Asn-Leu-Ser-Ser-Cys-Val-Leu-
Gly-Lys-Leu-Scr-Gln-Glu-Leu-His-Lys-Gln-
Thr-Tyr-Pro-Arg-Thr-Asp-Val-Gly-Ala-Gly-
-Thr-Pro-NH_2.

14. [16,19-Di-Alanine] Calcitonins having the following structures:

(a)

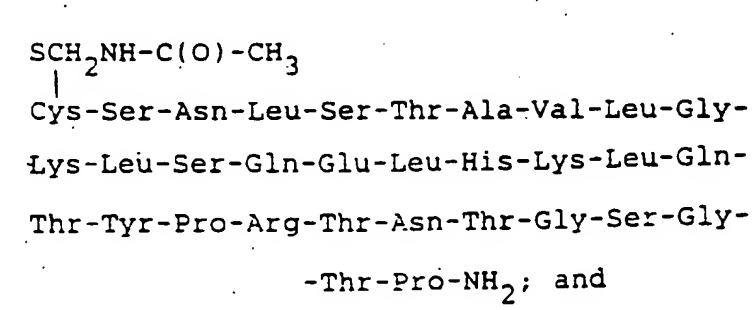


(b)

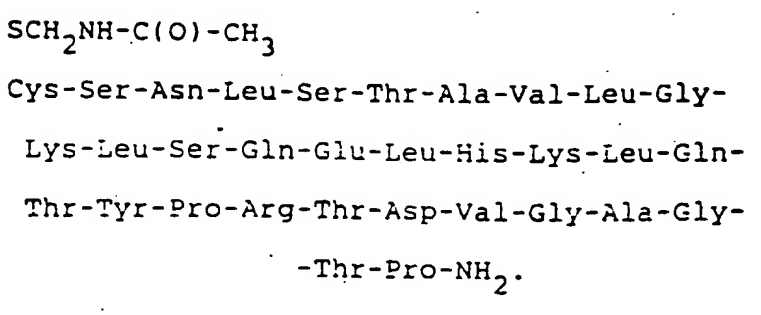


15. (1-S-Acetamidomethyl Systeine, 7-Alanine) Calcitonins having the following structures:

(a)

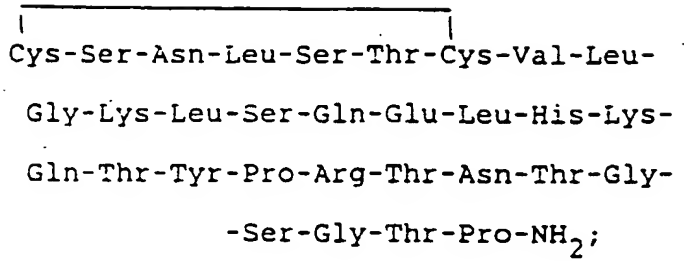


(b)

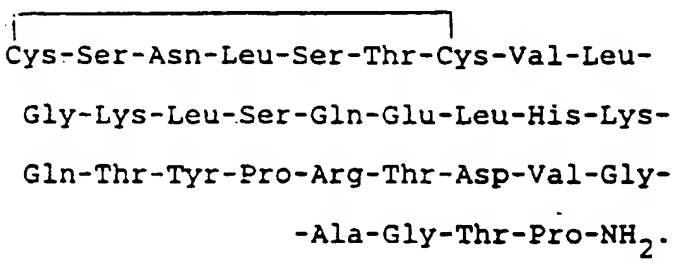


16. Des-19-Leucine - Calcitonin Analogs having the following structures:

(a)

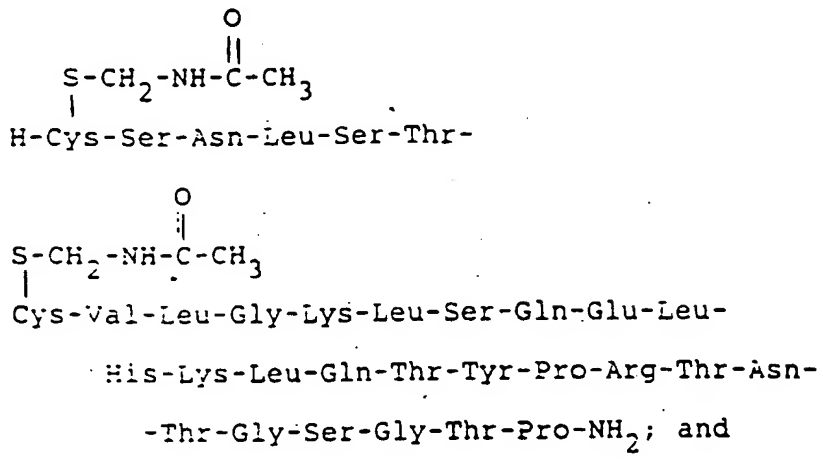

Cys-Ser-Asn-Leu-Ser-Thr-Cys-Val-Leu-
Gly-Lys-Leu-Ser-Gln-Glu-Leu-His-Lys-
Gln-Thr-Tyr-Pro-Arg-Thr-Asn-Thr-Gly-
-Ser-Gly-Thr-Pro-NH2;

(b)

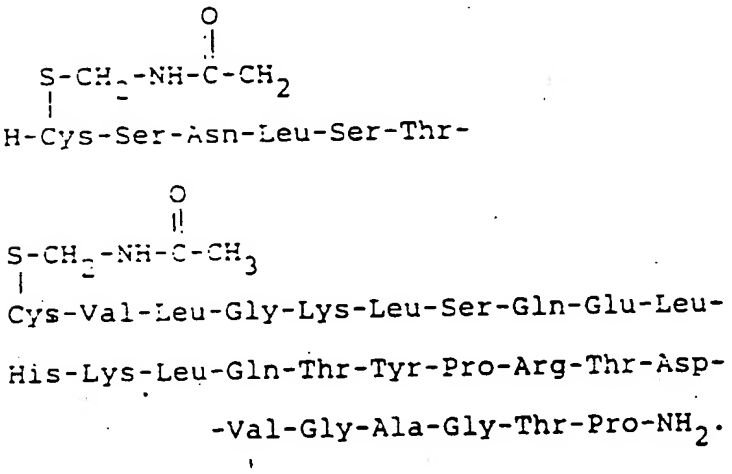

Cys-Ser-Asn-Leu-Ser-Thr-Cys-Val-Leu-
Gly-Lys-Leu-Ser-Gln-Glu-Leu-His-Lys-
Gln-Thr-Tyr-Pro-Arg-Thr-Asp-Val-Gly-
-Ala-Gly-Thr-Pro-NH2.

17. (Bis-1,7-S-Acetamidomethyl-L-Systeine) Salmon Calcitonins having the following structures:

(a)



(b)



18. 8-Glycine, Des-19-Leucine-Calcitonins having the following structures:

(a) Cys-Ser-Asn-Leu-Ser-Thr-Cys-Gly-Leu-Gly-
Lys-Leu-Ser-Gln-Glu-Leu-His-Lys-Gln-
Thr-Tyr-Pro-Arg-Thr-Asn-Thr-Gly-Ser-
-Gly-Thr-Pro-NH_2 (Salmon);

(b) Cys-Ser-Asn-Leu-Ser-Thr-Cys-Gly-Leu-Gly-
Lys-Leu-Ser-Gln-Glu-Leu-His-Lys-Gln-
Thr-Tyr-Pro-Arg-Thr-Asp-Val-Gly-Ala-
-Gly-Thr-Pro-NH_2 (Eel);
and

(c) Cys-Ala-Ser-Leu-Ser-Thr-Cys-Gly-Leu-Gly-
Lys-Leu-Ser-Gln-Glu-Leu-His-Lys-Gln-
Thr-Tyr-Pro-Arg-Thr-Asp-Val-Gly-Ala-
-Gly-Thr-Pro-NH_2 (Chicken).

19. Des-Leu[16]-Calcitonins having the following structures:

(a) Cys-Ser-Asn-Leu-Ser-Thr-Cys-Val-Leu-Gly-
Lys-Leu-Ser-Gln-Glu-His-
Lys-Leu-Gln-Thr-Tyr-Pro-Arg-
Thr-Asn-Thr-Gly-Ser-Gly-Thr-
-Pro-NH_2 (Salmon);

(b) Cys-Ser-Asn-Leu-Ser-Thr-Cys-Val-Leu-Gly-
Lys-Leu-Ser-Gln-Glu-His-
Lys-Leu-Gln-Thr-Tyr-Pro-Arg-
Thr-Asp-Val-Gly-Ala-Gly-Thr-
-Pro-NH_2 (Eel);

(c) Cys-Gly-Asn-Leu-Ser-Thr-Cys-Met-Leu-Gly-
Thr-Tyr-Thr-Gln-Asp-Asn-
Lys-Phe-His-Thr-Phe-Pro-Glu-
Thr-Ala-Ile-Gly-Val-Gly-Ala-
-Pro-NH_2 (Human).

20. Leucine ^{22}-Calcitonins having the following structures:

(a)

H-Cys-Ser-Asn-Leu-Ser-Thr-Cys-Val-Leu-Gly-
Lys-Leu-Ser-Gln-Glu-Leu-His-Lys-Leu-Gln-Thr-
Leu-Pro-Arg-Thr-Asn-Thr-Gly-Ser-Gly-Thr-Pro-
NH_2 (Salmon); and

(b)

H-Cys-Ser-Asn-Leu-Ser-Thr-Cys-Val-Leu-Gly-Lys-
Leu-Ser-Gln-Glu-Leu-His-Lys-Leu-Gln-Thr-Leu-Pro-
Arg-Thr-Asp-Val-Gly-Ala-Gly-Thr-Pro-NH_2 (Eel).

21. Glycine - 8 Calcitonins having the following structures:

(a)

H-Cys-Ser-Asn-Leu-Ser-Thr-Cys-Gly-Leu-Gly-Lys-
Leu-Ser-Gln-Glu-Leu-His-Lys-Leu-Gln-Thr-Tyr-
Pro-Arg-Thr-Asn-Thr-Gly-Ser-Gly-Thr-Pro-NH_2; and

(b)

Cys-Gly-Asn-Leu-Ser-Thr-Cys-Gly-Leu-Gly-Thr-
Tyr-Thr-Gln-Asp-Phe-Asn-Lys-Phe-His-Thr-Phe-Pro-
Gln-Thr-Ala-Ile-Gly-Val-Gly-Ala-Pro-NH_2.

22. Glycine^{8}-D-Arginine^{24} Calcitonins having the following structures:

(a)

H-Cys-Ser-Asn-Leu-Ser-Thr-Cys-Gly-
Leu-Gly-Lys-Leu-Ser-Gln-
Glu-Leu-His-Lys-Leu-Gln-Thr-
Tyr-Pro-D-ARG-Thr-Asn-Thr-Gly-
Ser-Gly-Thr-Pro-NH_2 (Salmon); and

(b)

H-Cys-Ser-Asn-Leu-Ser-Thr-Cys-Gly-
Leu-Gly-Lys-Leu-Ser-Gln-
Glu-Leu-His-Lys-Leu-Gln-Thr-
Tyr-Pro-D-ARG-Thr-Asp-Val-Gly-
Ala-Gly-Thr-Pro-NH_2 (Eel).

23. L-Tyrosine[21] Calcitonins having the following structures:

(a)

H-Cys-Ser-Asn-Leu-Ser-Thr-Cys-Val-
Leu-Gly-Lys-Leu-Ser-Gln-Glu-Leu-
His-Lys-Leu-Gln-Tyr-Tyr-Pro-Arg-
Thr-Asn-Thr-Gly-Ser-Gly-Thr-Pro-NH_2 (Salmon);
and

(b)

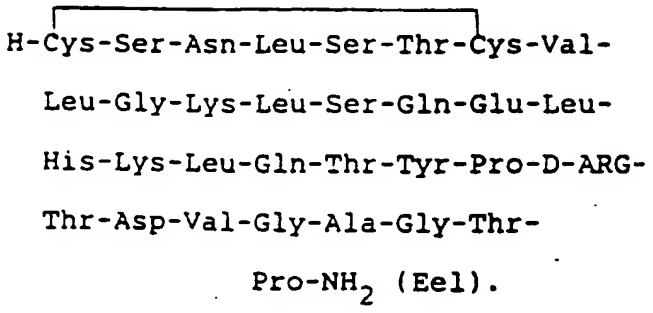
H-Cys-Ser-Asn-Leu-Ser-Thr-Cys-Val-
Leu-Gly-Lys-Leu-Ser-Gln-Glu-Leu-
His-Lys-Leu-Gln-Tyr-Tyr-Pro-Arg-
-Thr-Asp-Val-Gly-Ala-Gly-Thr-Pro-NH_2 (Eel).

24. D-Arginine[24] Calcitonins having the following structures:

(a)

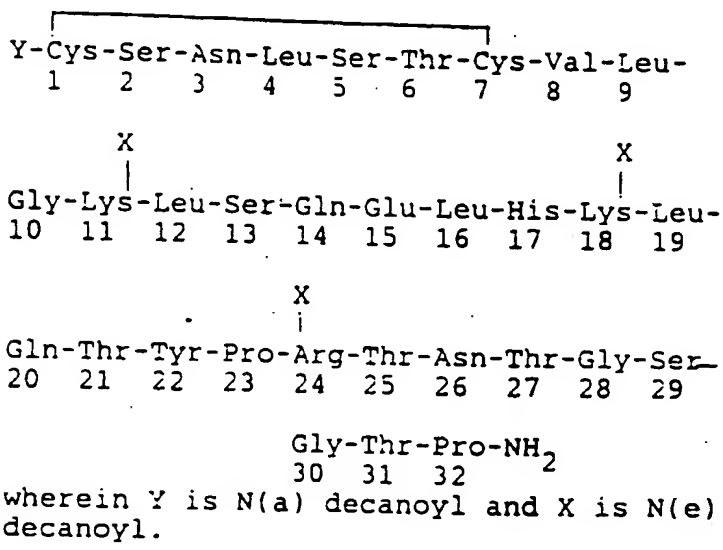
H-Cys-Ser-Asn-Leu-Ser-Thr-Cys-Val-
Leu-Gly-Lys-Leu-Ser-Gln-Glu-Leu-
His-Lys-Leu-Gln-Thr-Tyr-Pro-D-ARG-
Thr-Asn-Thr-Gly-Ser-Gly-Thr-
Pro-NH_2 (Salmon); and

(b)



25. Amides Analogues of Calcitonin having the following structures:

(a)



wherein Y is N(a) decanoyl and X is N(e) decanoyl.

26. [N-alpha, 1,7-Di-Alanine, Des-19-Leucine] Calcitonins having the following structures:

(a)

[N-alpha-X, 1,7 Di-Alanine (8-Y) Des-19-Leucine] calcitonins, wherein

X is H, free amino or acyl-amino wherein acyl is derived from a carboxylic acid having 1-10 carbon atoms, L-lactic acid or half amide of malonic, succinic, glutaric, or adipic acids, and

Y is L-valine, glycine, L-methonine, L-alanine, L-leucine or L-isoleucine; and

(b)

[N-alpha-X, 1, 7-Di-Alanine, Des-19-Leucine] calcitonins, wherein

X is an acyl derived from carboxylic acid having C_{1-5} carbon atoms.

27. 1,7-Di-Alanine, 8-Glycine, Des-19-Leucine Calcitonin having the following structure:

H_2N-Ala-Ser-Asn-Leu-Ser-Thr-Ala-Gly-Leu-Gly-
1 5 10

Lys-Leu-Ser-Gln-Glu-Leu-His-Lys-Gln-Thr-Tyr-
15 20

Pro-Arg-Thr-Asn-Thr-Gly-Ser-Gly-Thr-
25 30

Pro-(C=O)-NH_2.

28. N ∝ - Propionyl, 1,7-Di-Alanine, Des-19-Leucine Calcitonin having the following structure:

CH_3-CH_2-(C=O)-Hn-

Ala-Ser-Asn-Leu-Ser-Thr-Ala-Val-Leu-Gly-
1 5 10

Lys-Leu-Ser-Gln-Glu-Leu-His-Lys-Gln-Thr-Tyr-
15 20

Pro-Arg-Thr-Asn-Thr-Gly-Ser-Gly-Thr-Pro-
25 30

(C=O)-NH_2.

29. Further embodiment:

R_1 R_2
| |
Cys-Ser-Asn-Leu-Ser-Ser-Cys-Val-Leu-Gly-Lys-Leu-

Ser-Gln-Glu-Leu-His-Lys-Gln-Thr-Tyr-Pro-Arg-Thr-

Asn-Thr-Gly-Ser-Gly-Thr-Pro-NH_2;

where R_1 is S-n-alkyl, Cys or H and R_2 is S-n-alkyl or H, R_1 being S-n-alkyl, Cys or H when R_2 is H and R_2 being S-n-alkyl or H when R_1 is H.

Enhancement of intranasal delivery of calcitonin is effected by the presence of $^{\Delta}$-aminolevulinic acid in the formulations of the present invention.

$^{\Delta}$-aminolevulinic acid, having the formula:

H_2N-CH_2-C(O)-CH_2-CH_2-CO_2H, occurs naturally in the body, being derived from the condensation of glycine with succinyl-SCoA. It is known as a precursor of vitamins B_{12}, heme and chlorophyll. Its method of preparation is known in the art, for example, U.S. Patent No. 3,846,490.

The biologically/pharmacologically active calcitonins, as hereinbefore defined, and $^{\Delta}$-aminolevulinic acid will be formulated with one or more pharmaceutically acceptable excipients which result in a composition suitable for administering the calcitonin across the nasal membranes as a spray, nose drop or aerosol.

The diluent base or vehicle used in accordance with the present invention may be non-aqueous or aqueous. In the former case the group of diluents is the physiologically acceptable polar solvents. Preferred

compounds of this type are those with which it is possible to make a solution of adequate concentration of dissolved calcitonin. Examples of these agents are vegetable and mineral oils. If desired, such non-aqueous media may be mixed with water to form the diluent of the preparation. However, the degree of physiological acceptability of the non-aqueous diluents is generally less than that of aqueous media and the preferred diluent is therefore water without the addition of organic solvents.

Preferably, the subject calcitonin is formulated in water or a pharmaceutically acceptable aerosol composition. Nasal spray solutions are especially preferred with water or in buffer at a ph of between about 3.0 to 8.0, using a pharmaceutically acceptable buffer system. The buffer system of the present invention preferably contain a sodium or potassium phosphate/phosphoric acid buffer or a sodium or potassium acetate/acetic acid buffer or a sodium or potassium citrate/citric acid buffer in the range of 0.01 M to 0.5 M and preferably in the range of 0.05 M to 0.2 M. This concentration was found effective to provide stability of the dissolved calcitonin in the diluent base or vehicle.

The preparations of the present invention may also contain other additives, such as antioxidants, stabilizers, tonicity adjusters, viscosity builders and preservatives. The concentration of these additives may vary according to the particular additive used and the desired result sought. In general, the concentrations for these additives will be in the range as follows:

Additives	% W/V
Antioxidants	0.01 - 0.2
Stabilisers	0.01 - 2.0
Tonicity Adjuster	0.01 - 0.5
Viscosity Builders	0.1 - 2.0
Preservatives	0.001 - 2.0

The following will serve as illustration for two additives generally used in pharmaceutical preparations intended for similar purposes.

Preservatives	% W/V
Benzalkonium chloride	0.004 - 0.02
Disodium ethylene diamine tetraacetate	0.01 - 0.2
Thimerosal	0.001 - 0.01
Chlorobutanol	0.5 - 1.0
Methyl and/or propyl paraben	0.01 - 0.2
Phenethyl alcohol	0.25 - 0.75
Cyclohexedine	0.01 - 0.1

Viscosity Agents	% W/V
Methyl cellulose	0.1 - 2.0
Hydroxyethyl cellulose	0.1 - 2.0
Hydroxypropyl cellulose	0.1 - 2.0
Polyvinylpyrrolidone	0.5 - 2.0

Aerosol formulations and nose drops are prepared as per known techniques and composition profiles practiced in the art.

In preparing the formulations of the present invention, calcitonin may be dissolved in the vehicle or diluent after which the additional ingredients are added in accordance with customary formulation procedures known in the pharmaceutical industry.

Examples of typical intranasal formulations are set forth below.

EXAMPLE 1	% W/V
Calcitonin[1]	0.009
Δ-aminolevulinic acid	0.5
Gelatin	1.0
Purified water q.s.	100

EXAMPLE 2	% W/V
Calcitonin[1]	0.009
Δ-aminolevulinic acid	1.0
Gelatin	1.0
Purified water q.s.	100

EXAMPLE 3	% W/V
Calcitonin[1]	0.25
Δ-aminolevulinic acid	1.5
Sodium acetate $.3H_2O$	1.36
Acetic acid	0.6
Purified water q.s.	100

EXAMPLE 4	% W/V
Calcitonin[1]	0.5
Δ-aminolevulinic acid	2.0
Sodium acetate .$3H_2O$	1.36
Acetic acid	0.6
Purified water q.s.	100

EXAMPLE 5	% W/V
Calcitonin[1]	0.003
Δ-aminolevulinic acid	3.0
Sodium acetate .$3H_2O$	1.36
Acetic acid	0.6
Purified water q.s.	100

EXAMPLE 6	% W/V
Calcitonin[2]	0.25
Δ-aminolevulinic acid	1.0
Sodium citrate	1.36
Citric acid	0.6
Purified water q.s.	100

EXAMPLE 7	% W/V
Calcitonin[3]	0.50
Δ-aminolevulinic acid	2.0
Sodium phosphate	2.40
Citric acid	0.34
Thimerosal	0.002
Purified water q.s.	100

EXAMPLE 8	% W/V
Calcitonin[4]	2.0
Δ-aminolevulinic acid	0.5
Sodium acetate .$3H_2O$	1.36
Acetic acid	0.6
Benzalkonium chloride	0.01
Disodium ethylenediamine tetraacetate	0.1
Purified water q.s.	100

EXAMPLE 9	% W/V
Calcitonin[5]	5.00
Δ-aminolevulinic acid	3.00
Sodium acetate .$3H_2O$	1.36
Acetic acid	1.36
Chlorobutanol	0.1
Phenethyl alcohol	0.2
Purified water q.s.	100

EXAMPLE 10	% W/V
Calcitonin[6]	10.0
Δ-aminolevulinic acid	7.0
Sodium phosphate	2.40
Citric acid	0.34
Thimerosal	0.002
Purified water q.s.	100

EXAMPLE 11	Amount per 1 ml
Calcitonin[7]	1428.0 I.U.
Δ-aminolevulinic acid	10.0 mg
Benzalkonium chloride sodium, N.F., 50%	0.20 mg
Sodium acetate	2.95 mg
Acetic acid	9.84 mg
Hydrochloric acid, ACS (If needed)	To adjust pH to 4.0
Sodium hydroxide, ACS (If needed)	To adjust pH to 4.0
Water for injection, USP	q.s. to 1 ml

EXAMPLE 12	Amount per 1 ml
Calcitonin[7]	1428.0 I.U.
Δ-aminolevulinic acid	5.0 mg
Benzalkonium chloride sodium, N.F., 50%	0.20 mg
Sodium acetate	2.95 mg
Acetic acid	9.84 mg
Hydrochloric acid, ACS (If needed)	To adjust pH to 4.0
Sodium hydroxide, ACS (If needed)	To adjust pH to 4.0
Water for injection, USP	q.s. to 1 ml

EXAMPLE 13	Amount per 1 ml
Calcitonin[8]	1428.0 I.U.
Δ-aminolevulinic acid	10.0 mg
Benzalkonium chloride solution, N.F., 50%	0.20 mg

EXAMPLE 13 (cont'd)	Amount per 1 ml
Disodium EDTA, USP	1.00 mg
Citric acid monohydrate, USP	12.19 mg
Sodium citrate dihydrate, USP	12.37 mg
Hydrochloric acid, ACS (If needed)	To adjust pH to 4.0
Sodium hydroxide, ACS (If needed)	To adjust pH to 4.0
Water for injection, USP	q.s. to 1 ml

EXAMPLE 14	Amount per 1 ml
Calcitonin[8]	1428.0 I.U.
Δ-aminolevulinic acid	5.0 mg
Benzalkonium chloride solution, N.F., 50%	0.20 mg
Disodium EDTA, USP	1.00 mg
Citric acid monohydrate, USP	12.19 mg
Sodium citrate dihydrate, USP	12.37 mg
Hydrochloric acid, ACS (If needed)	To adjust pH to 4.0
Sodium hydroxide, ACS (If needed)	To adjust pH to 4.0
Water for injection, USP	q.s. to 1 ml

The gelatin used in the above formulations is a standard hydrolipid animal gelatin prepared for pharmaceutical use and routinely used as a diluent for peptides.

[1] Synthetic salmon calcitonin having a potency of 4,000 MRC (Medical Research Council) units.

2 Des asparagine-3-calcitonin; 4,300 MRC units/mg; USP 4,391,747.

3 IA-endo-glycine-calcitonin; 4,650 IU/mg; USP 4,497,732.

4 16-alanine calcitonin; 6,200 IU/mg; USP 4,528,132.

5 glycine^{8}-D-arginine^{24} calcitonin; 3,500 IU/mg; USP 4,414,149.

6 D-arginine^{24} calcitonin; 5,000 IU/mg; USP 4,469,632.

7 1,7-Di-alanine, 8-glycine, des-19-leucine calcitonin.

8 N$^{\alpha}$ - Propionyl, 1,7-di-alanine, des-19-leucine calcitonin.

Testing for Bioavailability

According to the present invention, it has been found that calcitonin can be administered intranasally from a vehicle containing $^{\Delta}$-aminolevulinic acid as peptidase inhibitor with results considerably superior to those obtained with the administration of calcitonin without $^{\Delta}$-aminolevulinic acid. The following study illustrates the bioavailability of calcitonin from the formulations of the present invention.

Formulations

The test formulations contained salmon calcitonin (from Armour Pharmaceutical Co., Fort Washington, PA) in amounts of 1.5 U/100 ul, yielding a dose of 5 U/kg when the dose volume administered to animals was 50 µl/150 g body weight. The formulations were made in 0.2M acetate buffer at pH 4.1 and also contained $^{\Delta}$-aminolevulinic acid in concentrations of 1 mg/ml, 5 mg/ml and 10 mg/ml.

The control formulations were the same as the test formulations but lacked $^{\Delta}$-aminolevulinic acid.

Protocol

Male Sprague-Dawley rats (Charles River CD strain) weighing approximately 150 g at the time of dosing were obtained from Charles River Breeding Laboratories (Wilmington, MA). The rats were fasted over-night before use, and water was given ad libitum.

The rats were anesthetized with an intraperitoneal injection of pentobarbital (50 mg/kg). An external jugular vein was cannulated to facilitate periodic blood sampling. Before dosing, the nasopalatine apertures were closed with an adhesive agent (Krazy Glue, Krazy Glue Inc., Itasca, IL). Throughout the experiment, the animals were kept immobilized in a supine position by taping the animal on a dissection board.

The rats were then administered an intra-nasal dose of SCT (5 U/kg, 50 µl/150 g) with or without the coadministration of $^{\Delta}$-aminolevulinic acid. The dosing was facilitated with the use of a micro-syringe (Hamilton Co., Reno, Nevada), and the dosing solution was delivered drop-wise into the nostril.

A volume of 0.7 ml of blood was drawn via the jugular cannula at 0 h, and at 1.0, 2.0, 3.0, and 4.0 h, post-dose. The samples were assayed for serum calcium according to an automated alizarin procedure as described by C.S. Fring et al., Clin. Chem., 16, 816 (1970).

The results are shown in Table I.

TABLE I

The Effect of Coadministration of Δ-Aminolevulinic Acid with an Intra-Nasal Dose of SCT (5 U/kg) on the Enhancement of Hypercalcemia in Rats

Concentration of Δ-Aminolevulinic Acid Acid	N[1]	Max Hypocalcemia ± S.D. (%)	Tmax[2] (h.)
Control	16	16.6 ± 8.2	2.0
(1 mg/ml)	14	25.2 ± 3.7	2.0
(5 mg/ml)	7	30.1 ± 3.3	3.0
(10 mg/ml)	8	26.7 ± 5.9	3.0

1) Number of animals

2) The time at which maximum hypocalcemia occurred.

Claims

1. An intranasal composition containing from 0.0001% W/V to 15% W/V of a polypeptide having a calcitonin activity; from 0.0005% W/V to 10% W/V of Δ-aminolevulinic acid; and a pharmaceutically acceptable excipient.

2. The intranasal composition of claim 1 wherein the composition contains from 0.0025% W/V to 10% W/V of a polypeptide having calcitonin activity; from 0.0025% W/V to 10% W/V of Δ-aminolevulinic acid; and a pharmaceutically acceptable excipient.

3. The intranasal composition of claim 1 or 2 wherein said polypeptide is salmon calcitonin or an analog thereof.

4. The intranasal composition of claim 1 or 2 wherein said polypeptide is selected from eel, bovin, porcine, ovine, rat, chicken, or human calcitonins.

5. The intranasal composition of any of claims 1 to 4 wherein said polypeptide has a potency of from 100 to 10,000 international units per mg of polypeptide.

6. The intranasal composition of claim 1 or 2 wherein said polypeptide is
[N-alpha-X, 1, 7 Di-Alanine (8-Y) Des-19-Leucine] calcitonin, wherein
X is H, free amino or acyl-amino wherein acyl is derived from a carboxylic acid having 1 to 10 carbon atoms, L-lactic acid or half amide of malonic, succinic, glutaric, or adipic acids, and

Y is L-valine, glycine, L-methonine, L-alanine, L-leucine or L isoleucine.

7. The intranasal composition of claim 1 or 2 wherein said polypeptide is: [N-alpha-X, 1, 7-Di-Alanine, Des-19-Leucine] calcitonin, wherein X is an acyl derived from carboxylic acid having C_{1-5} carbon atoms.

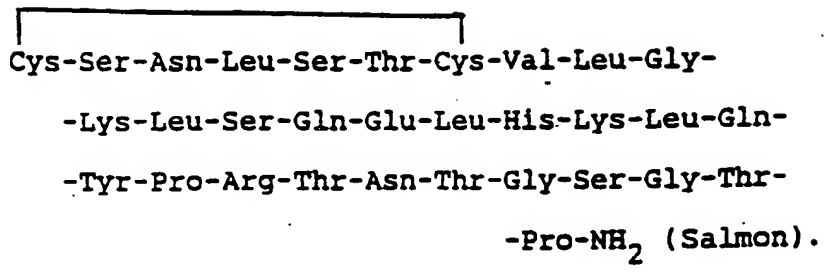
8. The intranasal composition of claim 1 or 2 wherein said polypeptide is:

H-Cys-Ser-Leu-Ser-Thr-Cys-Val-Leu-Gly-Lys-Leu-
Ser-Gln-Glu-Leu-His-Lys-Leu-Gln-Thr-Tyr-Pro-
Arg-Thr-Asn-Thr-Gly-Ser-Gly-Thr-Pro-NH_2

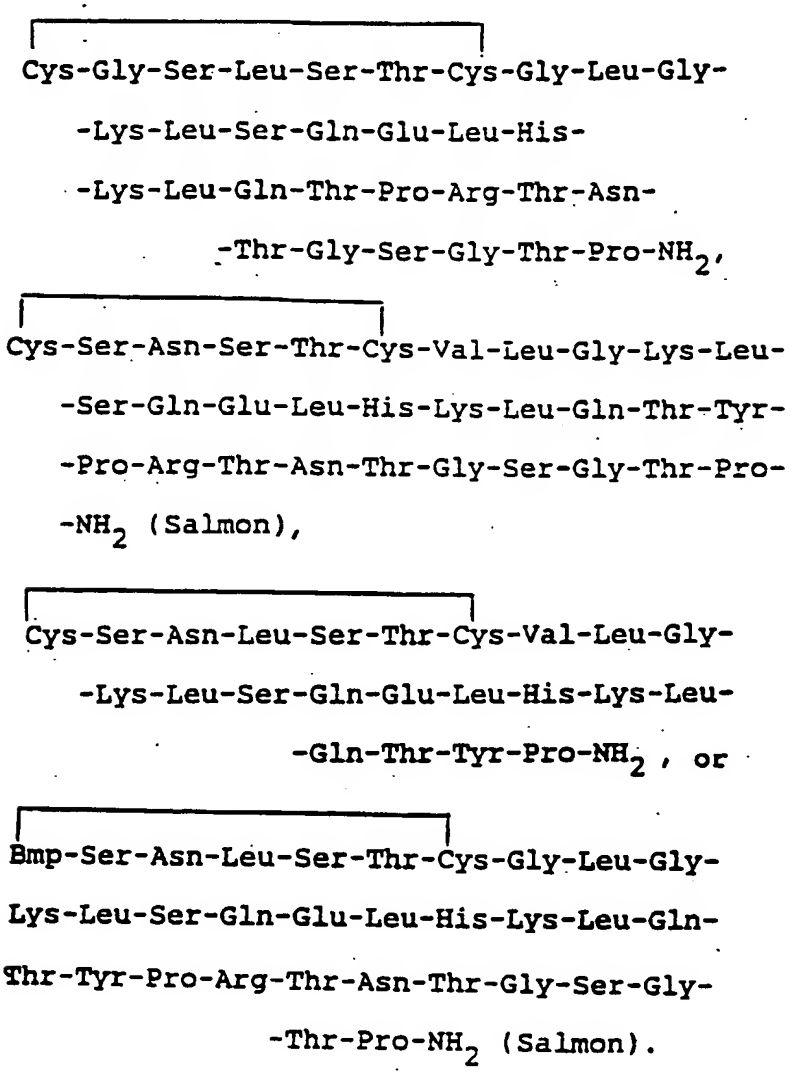
Cys-Ser-Asn-Leu-Ser-Thr-Cys-Val-Leu-Gly-
-Lys-Leu-Ser-Gln-Glu-Ala-His-Lys-Leu-Gln-
-Thr-Tyr-Pro-Arg-Thr-Asn-Thr-Gly-Ser-Gly-
-Thr-Pro-NH_2 (Salmon),

H-Cys-Asn-Leu-Ser-Thr-Cys-Gly-Leu-
-Gly-Lys-Leu-Ser-Gln-Glu-Leu-His-
-Lys-Leu-Gln-Thr-Pro-Arg-Thr-Asn-
-Thr-Gly-Ser-Gly-Thr-Pro-NH_2 (Salmon),

Cys-Ser-Asn-Leu-Ser-Thr-Cys-Val-Leu-Gly-
-Lys-Leu-Gln-Glu-Leu-His-Lys-
-Leu-Gln-Thr-Tyr-Pro-Arg-Thr-Asn-
-Thr-Gly-Ser-Gly-Thr-Pro-NH_2, or



9. The intranasal composition of claim 1 or 2 wherein said polypeptide is:



10. The intranasal composition of claim 1 or 2 wherein said polypeptide is:

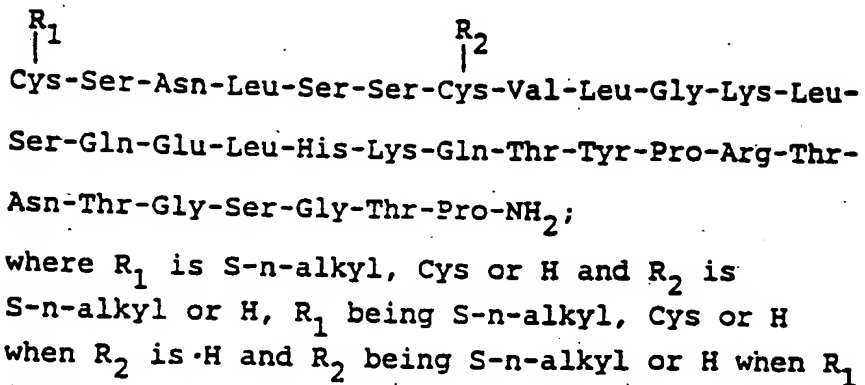
Ala-Ser-Asn-Leu-Ser-Thr-Ala-Val-Leu-Gly-Lys-
Leu-Ser-Gln-Glu-Ala-His-Lys-Leu-Gln-Thr-Tyr-
Pro-Arg-Thr-Asn-Thr-Gly-Ser-Gly-Thr-Pro-NH_2 ,

Cys-Ser-Asn-Leu-Ser-Thr-Cys-Met-Leu-
Gly-Lys-Leu-Ser-Gln-Glu-Leu-His-Lys-
Leu-Gln-Thr-Tyr-Pro-Arg-Thr-Asn-Thr-
Gly-Ser-Gly-Thr-Pro-NH_2 ,

Cys-Leu-Ser-Thr-Cys-Val-Leu-Gly-Lys-
Leu-Ser-Gln-Glu-Leu-His-Lys-Leu-Gln-
Thr-Tyr-Pro-Arg-Thr-Asn-Thr-Gly-Ser-
Gly-Thr-Pro-NH_2 , or

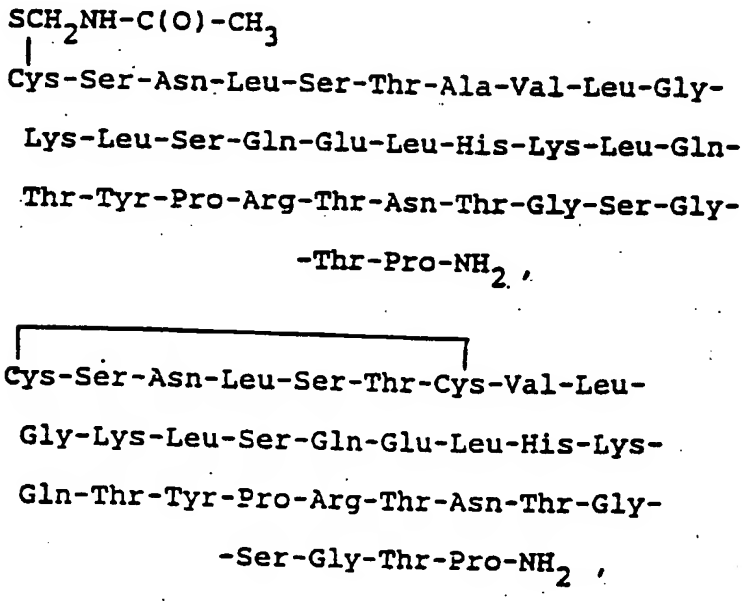
Cys-Ser-Asn-Leu-Ser-Ser-Cys-Val-Leu-Gly-
Lys-Leu-Ser-Gln-Glu-Leu-His-Lys-Gln-Thr-
Tyr-Pro-Arg-Thr-Asn-Thr-Gly-Ser-
-Gly-Thr-Pro-NH_2.

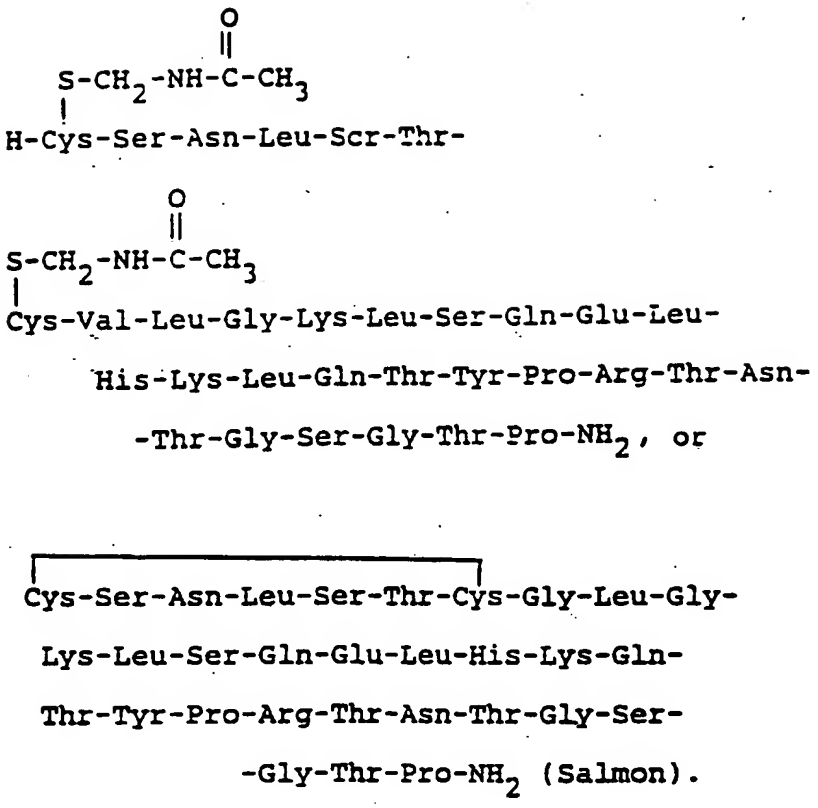
11. The intranasal composition of claim 1 or 2 wherein said polypeptide is:



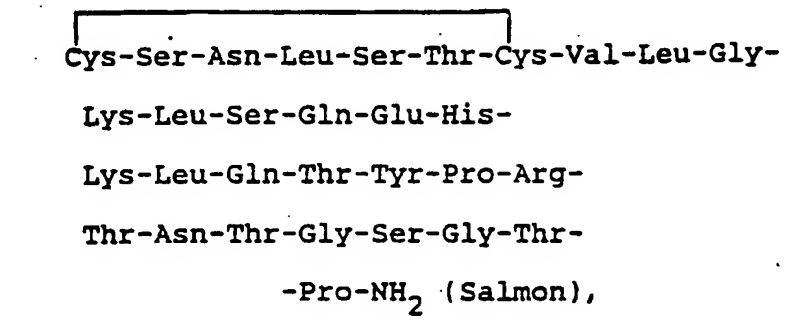
where R_1 is S-n-alkyl, Cys or H and R_2 is S-n-alkyl or H, R_1 being S-n-alkyl, Cys or H when R_2 is H and R_2 being S-n-alkyl or H when R_1 is H.

12. The intranasal composition of claim 1 or 2 wherein said polypeptide is:





13. The intranasal composition of claim 1 or 2 wherein said polypeptide is:



H-Cys-Ser-Asn-Leu-Ser-Thr-Cys-Val-Leu-Gly-
Lys-Leu-Ser-Gln-Glu-Leu-His-Lys-Leu-Gln-Thr-
Leu-Pro-Arg-Thr-Asn-Thr-Gly-Ser-Gly-Thr-Pro-
NH_2 (Salmon),

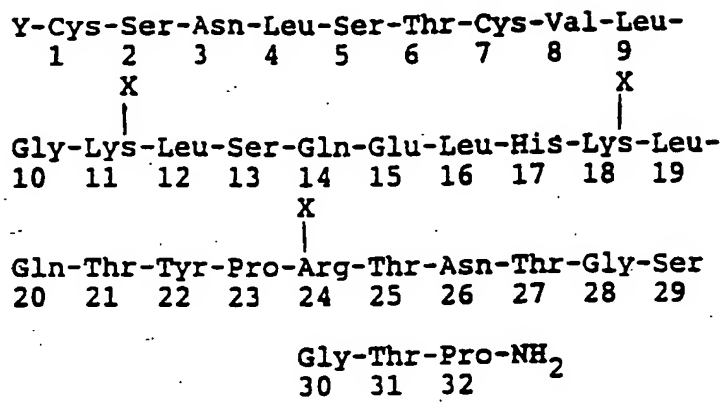
H-Cys-Ser-Asn-Leu-Ser-Thr-Cys-Gly-Leu-Gly-Lys-
Leu-Ser-Gln-Glu-Leu-His-Lys-Leu-Gln-Thr-Tyr-
Pro-Arg-Thr-Asn-Thr-Gly-Ser-Gly-Thr-Pro-NH_2 ,

H-Cys-Ser-Asn-Leu-Ser-Thr-Cys-Gly-
Leu-Gly-Lys-Leu-Ser-Gln-
Glu-Leu-His-Lys-Leu-Gln-Thr-
Tyr-Pro-D-ARG-Thr-Asn-Thr-Gly-
Ser-Gly-Thr-Pro-NH_2 (Salmon),

H-Cys-Ser-Asn-Leu-Ser-Thr-Cys-Val-
Leu-Gly-Lys-Leu-Ser-Gln-Glu-Leu-
His-Lys-Leu-Gln-Tyr-Tyr-Pro-Arg-
Thr-Asn-Thr-Gly-Ser-Gly-Thr-Pro-NH_2 (Salmon), or

H-Cys-Ser-Asn-Leu-Ser-Thr-Cys-Val-
Leu-Gly-Lys-Leu-Ser-Gln-Glu-Leu-
His-Lys-Leu-Gln-Thr-Tyr-Pro-D-ARG-
Thr-Asn-Thr-Gly-Ser-Gly-Thr-
Pro-NH_2 (Salmon).

14. The intranasal composition of claim 1 or 2 wherein said polypeptide is:



wherein Y is N(a) decanoyl and X is N(e) decanoyl.

15. The intranasal composition of claim 1 or 2 wherein said polypeptide is:

H_2N-Ala-Ser-Asn-Leu-Ser-Thr-Ala-Gly-Leu-Gly-
1 5 10

Lys-Leu-Ser-Gln-Glu-Leu-His-Lys-Gln-Thr-Tyr-
15 20

Pro-Arg-Thr-Asn-Thr-Gly-Ser-Gly-Thr-
25 30

Pro-(C=O)-NH_2.

16. The intranasal composition of claim 1 or 2 wherein said polypeptide is:

CH_3-CH_2-(C=O)-Hn-

Ala-Ser-Asn-Leu-Ser-Thr-Ala-Val-Leu-Gly-
1 5 10

Lys-Leu-Ser-Gln-Glu-Leu-His-Lys-Gln-Thr-Tyr-
15 20

Pro-Arg-Thr-Asn-Thr-Gly-Ser-Gly-Thr-Pro-
25 30

(C=O)-NH_2.

17. A method for enhancing the bioavailability of a polypeptide having calcitonin activity comprising: adding from 0.0005% W/V to 10% W/V of Δ-aminolevulinic acid to a composition comprising 0.0001% W/V to 15% W/V of a polypeptide having calcitonin activity and a pharmaceutically acceptable excipient.

18. The use of Δ-aminolevulinic acid to prepare an intranasal composition containing from 0.0001% W/V to 15% W/V of a polypeptide having calcitonin activity; from 0.0005% W/V to 10% W/V of Δ-aminolevulinic acid; and a pharmaceutically acceptable excipient.

19. The use of Δ-aminolevulinic acid to prepare an intranasal composition for treating hyperathyroidism, idiopathic hypercalcemia of infancy, Paget's disease, vitamin D intoxication or osteolyptic bone metastases said diseases being characterized by hypercalcemia and high phosphate concentrations in the blood, the intranasal composition being defined in any of claims 1 to 16.

Patentansprüche

1. Intranasale Zusammensetzung, die von 0,0001 % Gew./Vol. bis 15 % Gew./Vol. eines Polypeptids mit Calcitoninaktivität, von 0,0005 % Gew./Vol. bis 10% Gew./Vol. Δ-Aminolaevulinsäure und einen pharmzeutisch akzeptablen Träger enthält.

2. Intranasale Zusammensetzung nach Anspruch 1, worin die Zusammensetzung von 0,0025 % Gew./Vol bis 10 % Gew./Vol. eines Polypeptids mit Calcitoninaktivität, von 0,0025 % Gew./Vol. bis 10 % Gew./Vol. Δ-Aminolaevulinsäure und einen pharmazeutisch akzeptablen Träger enthält.

3. Intranasale Zusammensetzung nach Anspruch 1 oder 2, worin das Polypeptid Lachscalcitonin oder eine analoge Verbindung davon ist.

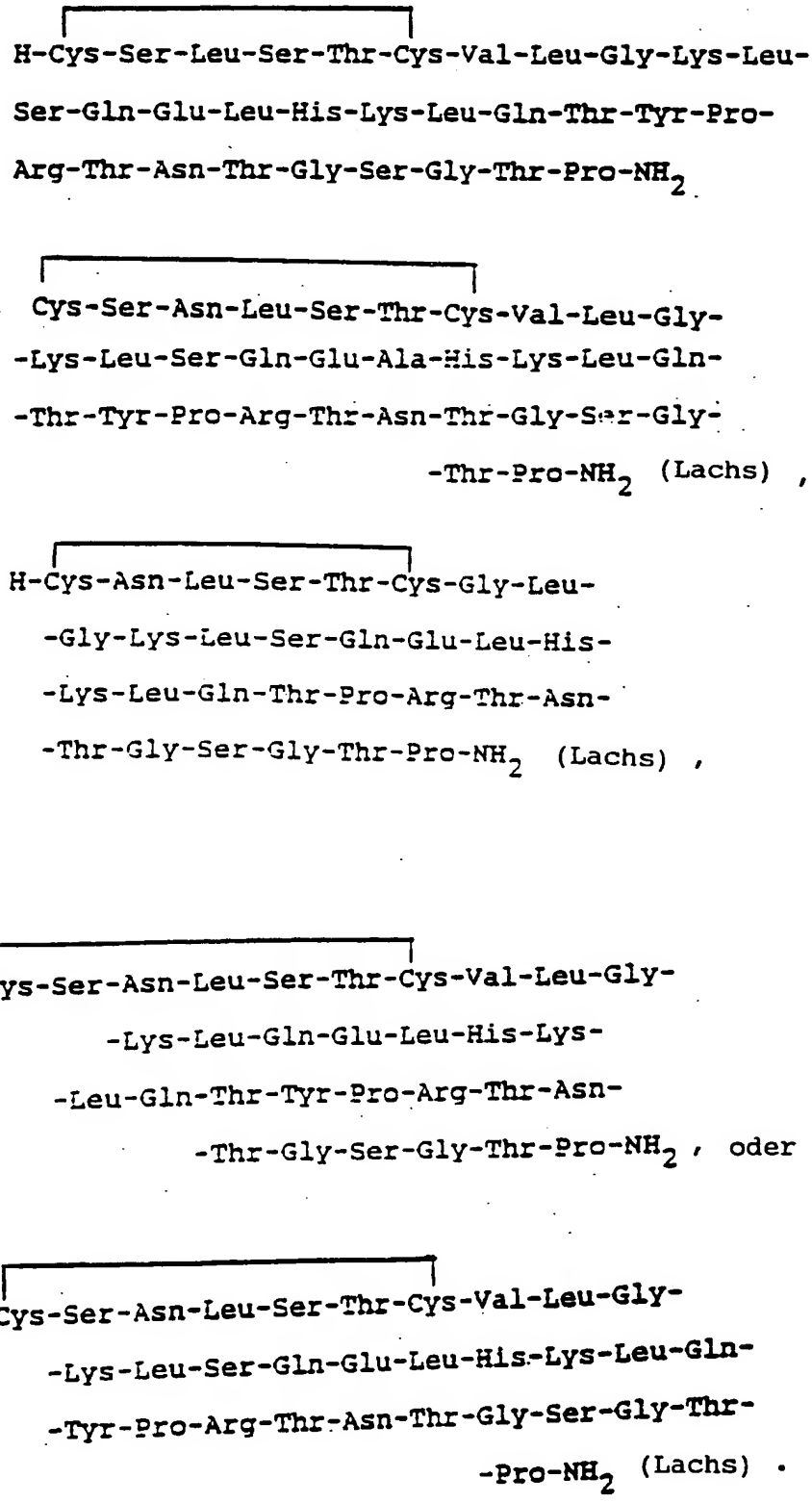
4. Intranasale Zusammensetzung nach Anspruch 1 oder 2, worin das Polypeptid aus Aal-, Rinder-, Schweine-, Schaf-, Ratten-, Hühner- oder menschlichen Calcitoninen ausgewählt ist.

5. Intranasale Zusammensetzung nach einem der Ansprüche 1 bis 4, worin das Polypeptid eine Wirksamkeit von 100 bis 10000 I.E. pro mg Polypeptid hat.

6. Intranasale Zusammensetzung nach Anspruch 1 oder 2, worin das Polypeptid [N-alpha-X, 1,7-Di-Alanin (8-Y) Des-19-Leucin]calcitonin ist, worin X H, eine freie Amino- oder Acylaminogruppe, worin Acyl abgeleitet ist von einer Carbonsäure mit 1 bis 10 Kohlenstoffatomen, L-Milchsäure oder ein Halbamid von Malonsäure, Bernsteinsäure, Glutarsäure oder Adipinsäure ist und Y L-Valin, Glycin, L-Methonin, L-Alanin, L-Leucin oder L-Isoleucin ist.

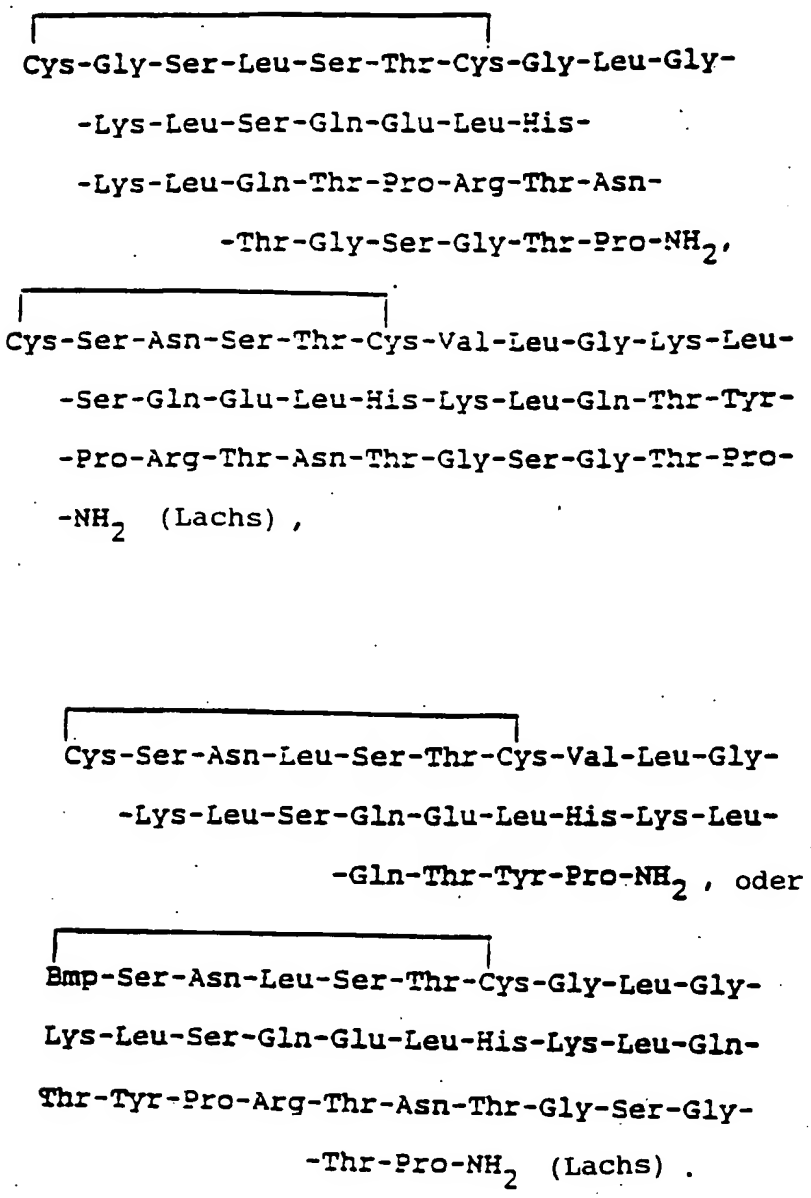
7. Intranasale Zusammensetzung nach Anspruch 1 oder 2, worin das Polypeptid [N-alpha-X, 1,7-Di-Alanin, Des-19-Leucin]calcitonin ist, worin X eine Acylgruppe ist, die von einer Carbonsäure mit 1 bis 5 Kohlenstoffatomen abgeleitet ist.

8. Intranasale Zusammensetzung nach Anspruch 1 oder 2, worin das polypeptid



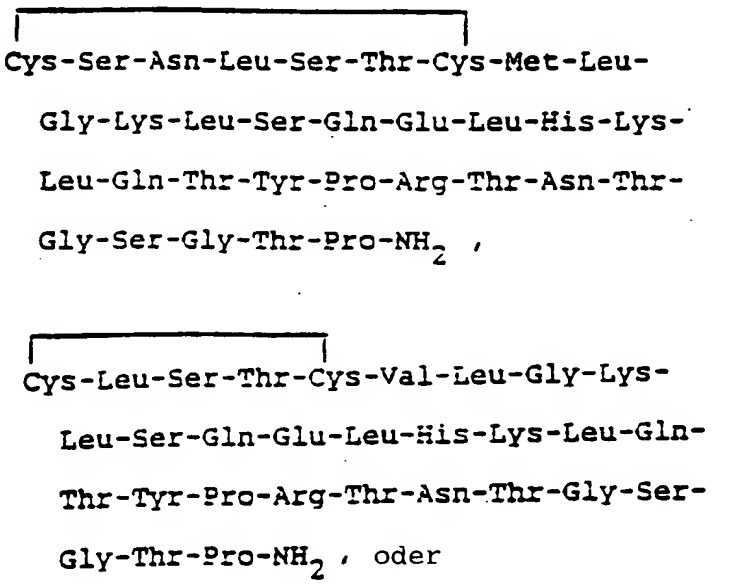
ist.

9. Intranasale Zusammensetzung nach Anspruch 1 oder 2, worin das Polypeptid



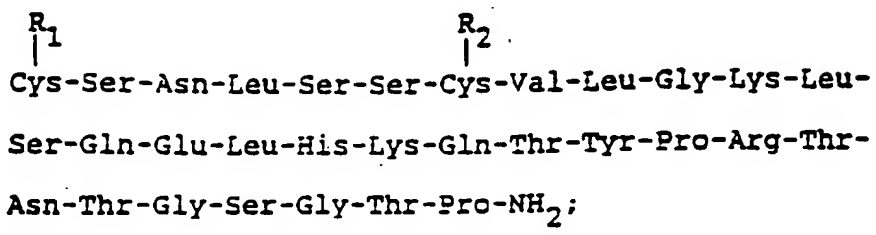
ist.

10. Intranasale Zusammensetzung nach Anspruch 1 oder 2, worin das Polypeptid



ist.

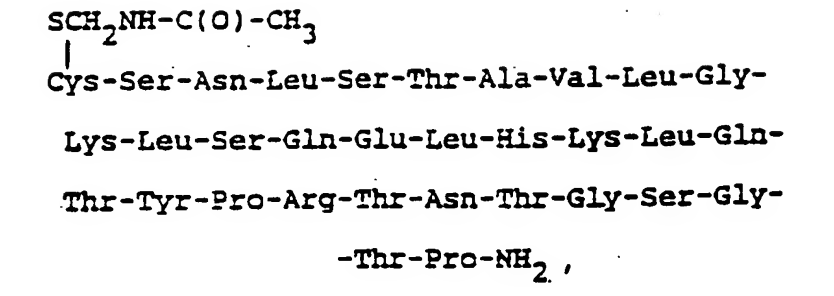
11. Intranasale Zusammensetzung nach Anspruch 1 oder 2, worin das Polypeptid

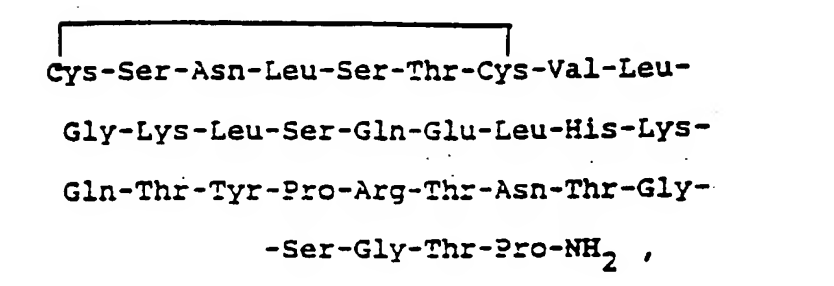


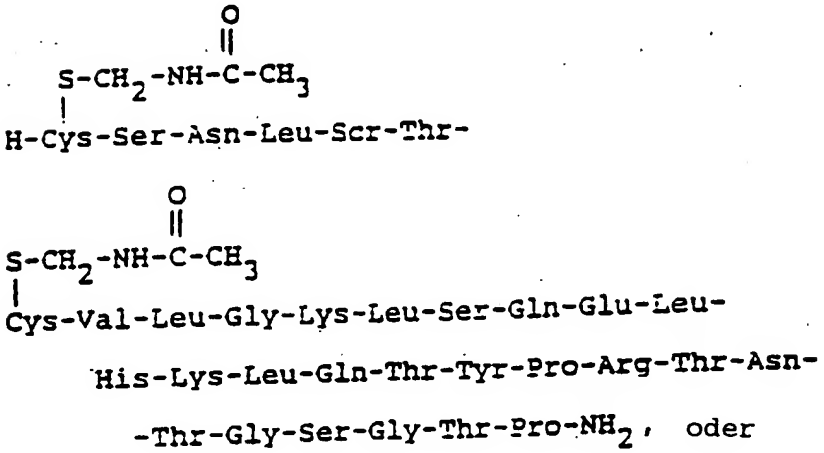
ist; worin R_1 S-n-Alkyl, Cys oder H ist und R_2 S-n-Alkyl oder H ist, wobei R_1 S-n-Alkyl, Cys oder H ist,

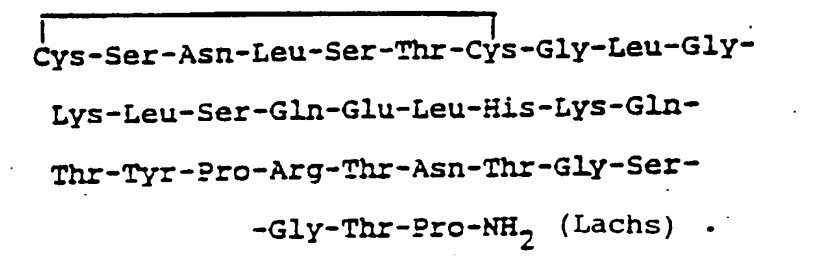
wenn R_2 H ist und R_2 S-n-Alkyl oder H ist, wenn R_1 H ist.

12. Intranasale Zusammensetzung nach Anspruch 1 oder 2, worin das Polypeptid


SCH2NH-C(O)-CH3
Cys-Ser-Asn-Leu-Ser-Thr-Ala-Val-Leu-Gly-
Lys-Leu-Ser-Gln-Glu-Leu-His-Lys-Leu-Gln-
Thr-Tyr-Pro-Arg-Thr-Asn-Thr-Gly-Ser-Gly-
-Thr-Pro-NH2 ,


Cys-Ser-Asn-Leu-Ser-Thr-Cys-Val-Leu-
Gly-Lys-Leu-Ser-Gln-Glu-Leu-His-Lys-
Gln-Thr-Tyr-Pro-Arg-Thr-Asn-Thr-Gly-
-Ser-Gly-Thr-Pro-NH2 ,


O
S-CH2-NH-C-CH3
H-Cys-Ser-Asn-Leu-Scr-Thr-
O
S-CH2-NH-C-CH3
Cys-Val-Leu-Gly-Lys-Leu-Ser-Gln-Glu-Leu-
His-Lys-Leu-Gln-Thr-Tyr-Pro-Arg-Thr-Asn-
-Thr-Gly-Ser-Gly-Thr-Pro-NH2 , oder


Cys-Ser-Asn-Leu-Ser-Thr-Cys-Gly-Leu-Gly-
Lys-Leu-Ser-Gln-Glu-Leu-His-Lys-Gln-
Thr-Tyr-Pro-Arg-Thr-Asn-Thr-Gly-Ser-
-Gly-Thr-Pro-NH2 (Lachs) .

ist.

13. Intranasale Zusammensetzung nach Anspruch 1 oder 2, worin das Polypeptid

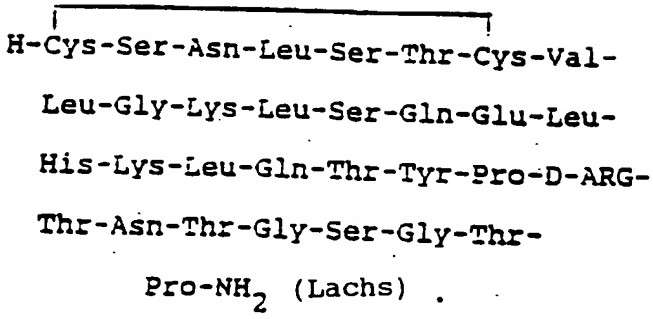
Cys-Ser-Asn-Leu-Ser-Thr-Cys-Val-Leu-Gly-
Lys-Leu-Ser-Gln-Glu-His-
Lys-Leu-Gln-Thr-Tyr-Pro-Arg-
Thr-Asn-Thr-Gly-Ser-Gly-Thr-
-Pro-NH_2 (Lachs),

H-Cys-Ser-Asn-Leu-Ser-Thr-Cys-Val-Leu-Gly-
Lys-Leu-Ser-Gln-Glu-Leu-His-Lys-Leu-Gln-Thr-
Leu-Pro-Arg-Thr-Asn-Thr-Gly-Ser-Gly-Thr-Pro-
NH_2 (Salmon),

H-Cys-Ser-Asn-Leu-Ser-Thr-Cys-Gly-Leu-Gly-Lys-
Leu-Ser-Gln-Glu-Leu-His-Lys-Leu-Gln-Thr-Tyr-
Pro-Arg-Thr-Asn-Thr-Gly-Ser-Gly-Thr-Pro-NH_2,

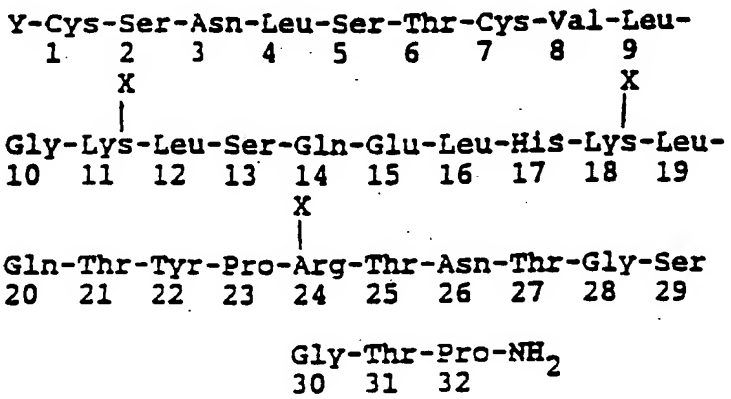
H-Cys-Ser-Asn-Leu-Ser-Thr-Cys-Gly-
Leu-Gly-Lys-Leu-Ser-Gln-
Glu-Leu-His-Lys-Leu-Gln-Thr-
Tyr-Pro-D-ARG-Thr-Asn-Thr-Gly-
Ser-Gly-Thr-Pro-NH_2 (Lachs),

H-Cys-Ser-Asn-Leu-Ser-Thr-Cys-Val-
Leu-Gly-Lys-Leu-Ser-Gln-Glu-Leu-
His-Lys-Leu-Gln-Tyr-Tyr-Pro-Arg-
Thr-Asn-Thr-Gly-Ser-Gly-Thr-Pro-NH_2 (Lachs) oder



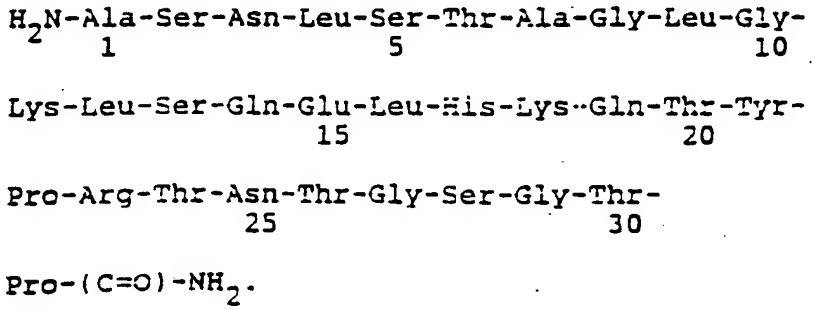
ist.

14. Intranasale Zusammensetzung nach Anspruch 1 oder 2, worin das Polypeptid



ist, worin Y N(a) Decanoyl und X N(e) Decanoyl ist.

15. Intranasale Zusammensetzung nach Anspruch 1 oder 2, worin das Polypeptid



ist.

16. Intranasale Zusammensetzung nach Anspruch 1 oder 2, worin das Polypeptid

$CH_3-CH_2-(C=O)-Hn-$

Ala-Ser-Asn-Leu-Ser-Thr-Ala-Val-Leu-Gly-
1 5 10

Lys-Leu-Ser-Gln-Glu-Leu-His-Lys-Gln-Thr-Tyr-
15 20

Pro-Arg-Thr-Asn-Thr-Gly-Ser-Gly-Thr-Pro-
25 30

$(C=O)-NH_2$.

ist.

17. Verfahren zur Verstärkung der Bioverfügbarkeit eines Polypeptids mit Calcitoninaktivität, das das Zufügen von 0,0005 % Gew.-Vol. bis 10 % Gew./Vol. Δ-Aminolaevulinsäure zu einer Zusammensetzung, umfassend 0,0001 % Gew./Vol. bis 15 % Gew./Vol. eines Polypeptids mit Calcitoninaktivität und einen pharmazeutisch akzeptablen Träger, umfaßt.

18. Verwendung von Δ-Aminolaevulinsäure, um eine intranasale Zusammensetzung herzustellen, die von 0,0001 % Gew./Vol. bis 15 % Gew./Vol. eines Polypeptids mit Calcitoninaktivität, von 0,0005 % Gew./Vol. bis 10 % Gew./Vol. Δ-Aminolaevulinsäure und einen pharmazeutisch akzeptablen Träger enthält.

19. Verwendung von is Δ-Aminolaevulinsäure, um eine intranasale Zusammensetzung zur Behandlung von Hyperathyreose, idiopathischer Hypercalcämie bei Kindern, Paget Carcinom, Vitamin D Intoxikation oder osteolytischer Knochenmetastasen herzustellen, wobei diese Krankheiten durch Hypercalcämie und hohe Phosphatkonzentrationen im Blut gekennzeichnet sind und die intranasale Zusammensetzung wie in einem der Ansprüche 1 bis 16 definiert ist.

Revendications

1. Composition intranasale contenant :
   - de 0,0001% p/v à 15% p/v d'un polypeptide ayant une activité de calcitonine ;
   - de 0,0005% p/v à 10% p/v d'acide Δ-aminolévulinique : et
   - un excipient pharmaceutiquement acceptable.

2. Composition intranasale selon la revendication 1, dans laquelle la composition contient :
   - de 0,0025% p/v à 10% p/v d'un polypeptide ayant une activité de calcitonine ;
   - de 0,0025% p/v à 10% p/v d'acide Δ-aminolévulinique ; et
   - un excipient pharmaceutiquement acceptable.

3. Composition intranasale selon l'une des revendications 1 ou 2, dans laquelle ledit polypeptide est la calcitonine de saumon ou un analogue de celle-ci.

4. Composition intranasale selon l'une des revendications 1 ou 2, dans laquelle ledit polypeptide est choisi parmi les calcitonines d'anguille, bovine, porcine, ovine, de rat, de poulet, ou humaine.

5. Composition intranasale selon l'une quelconque des revendications 1 à 4, dans laquelle ledit polypeptide a une puissance se situant dans la plage de 100 à 10 000 unités internationales par mg de polypeptide.

6. Composition intranasale selon l'une des revendications 1 ou 2, dans laquelle ledit polypeptide est : [N-alpha-X, 1,7-Di-Alanine (8-Y) Des-19-Leucine] calcitonine,
dans laquelle :
- X représente H, amino libre ou acyl-amino, où acyle est issu d'un acide carboxylique ayant 1 à 10 atomes de carbone, de l'acide L-lactique ou d'un semi-amide des acides malonique, succinique, glutarique ou adipique ; et
- Y représente L-valine, glycine, L-méthionine, L-alanine, L-leucine ou L-isoleucine.

7. Composition intranasale selon l'une des revendications 1 ou 2, dans laquelle ledit polypeptide est : [N-alpha-X, 1,7-Di-Alanine, Des-19-Leucine] calcitonine, dans laquelle :
- X est un acyle issu d'un acide carboxylique ayant 1 à 5 atomes de carbone.

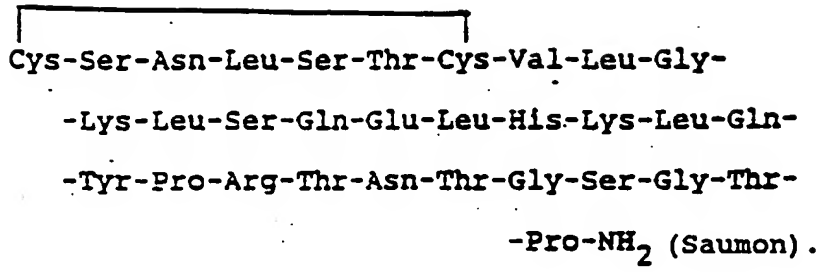
8. Composition intranasale selon l'une des revendications 1 ou 2, dans laquelle ledit polypeptide est :

H-Cys-Ser-Leu-Ser-Thr-Cys-Val-Leu-Gly-Lys-Leu-
Ser-Gln-Glu-Leu-His-Lys-Leu-Gln-Thr-Tyr-Pro-
Arg-Thr-Asn-Thr-Gly-Ser-Gly-Thr-Pro-NH_2.

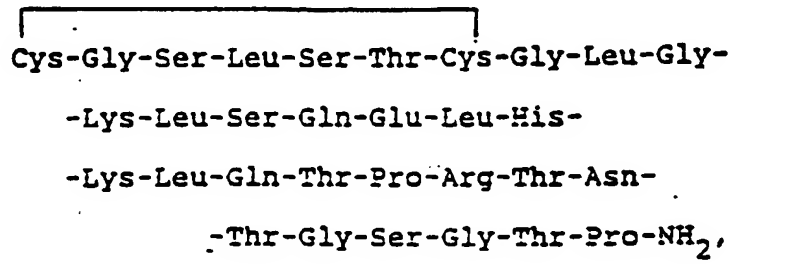
Cys-Ser-Asn-Leu-Ser-Thr-Cys-Val-Leu-Gly-
-Lys-Leu-Ser-Gln-Glu-Ala-His-Lys-Leu-Gln-
-Thr-Tyr-Pro-Arg-Thr-Asn-Thr-Gly-Ser-Gly-
-Thr-Pro-NH_2 (Saumon)

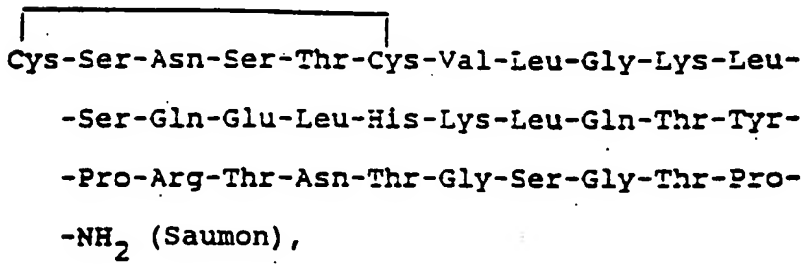
H-Cys-Asn-Leu-Ser-Thr-Cys-Gly-Leu-
-Gly-Lys-Leu-Ser-Gln-Glu-Leu-His-
-Lys-Leu-Gln-Thr-Pro-Arg-Thr-Asn-
-Thr-Gly-Ser-Gly-Thr-Pro-NH_2 (Saumon)

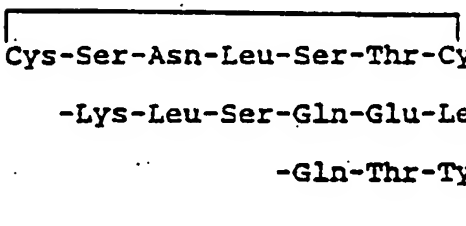
Cys-Ser-Asn-Leu-Ser-Thr-Cys-Val-Leu-Gly-
-Lys-Leu-Gln-Glu-Leu-His-Lys-
-Leu-Gln-Thr-Tyr-Pro-Arg-Thr-Asn-
-Thr-Gly-Ser-Gly-Thr-Pro-NH_2, ou

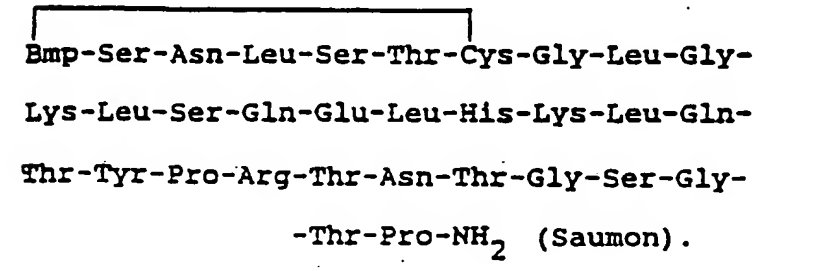


9. Composition intranasale selon l'une des revendications 1 ou 2, dans laquelle ledit polypeptide est :









10. Composition intranasale selon l'une des revendications 1 ou 2, dans laquelle ledit polypeptide est :

Ala-Ser-Asn-Leu-Ser-Thr-Ala-Val-Leu-Gly-Lys-
Leu-Ser-Gln-Glu-Ala-His-Lys-Leu-Gln-Thr-Tyr-
Pro-Arg-Thr-Asn-Thr-Gly-Ser-Gly-Thr-Pro-NH_2 ,

Cys-Ser-Asn-Leu-Ser-Thr-Cys-Met-Leu-
Gly-Lys-Leu-Ser-Gln-Glu-Leu-His-Lys-
Leu-Gln-Thr-Tyr-Pro-Arg-Thr-Asn-Thr-
Gly-Ser-Gly-Thr-Pro-NH_2 ,

Cys-Leu-Ser-Thr-Cys-Val-Leu-Gly-Lys-
Leu-Ser-Gln-Glu-Leu-His-Lys-Leu-Gln-
Thr-Tyr-Pro-Arg-Thr-Asn-Thr-Gly-Ser-
Gly-Thr-Pro-NH_2 , ou

Cys-Ser-Asn-Leu-Ser-Ser-Cys-Val-Leu-Gly-
Lys-Leu-Ser-Gln-Glu-Leu-His-Lys-Gln-Thr-
Tyr-Pro-Arg-Thr-Asn-Thr-Gly-Ser-
-Gly-Thr-Pro-NH_2.

11. Composition intranasale selon l'une des 5 revendications 1 ou 2, dans laquelle ledit polypeptide est :

R_1 R_2
Cys-Ser-Asn-Leu-Ser-Ser-Cys-Val-Leu-Gly-Lys-Leu-
Ser-Gln-Glu-Leu-His-Lys-Gln-Thr-Tyr-Pro-Arg-Thr-
Asn-Thr-Gly-Ser-Gly-Thr-Pro-NH_2;

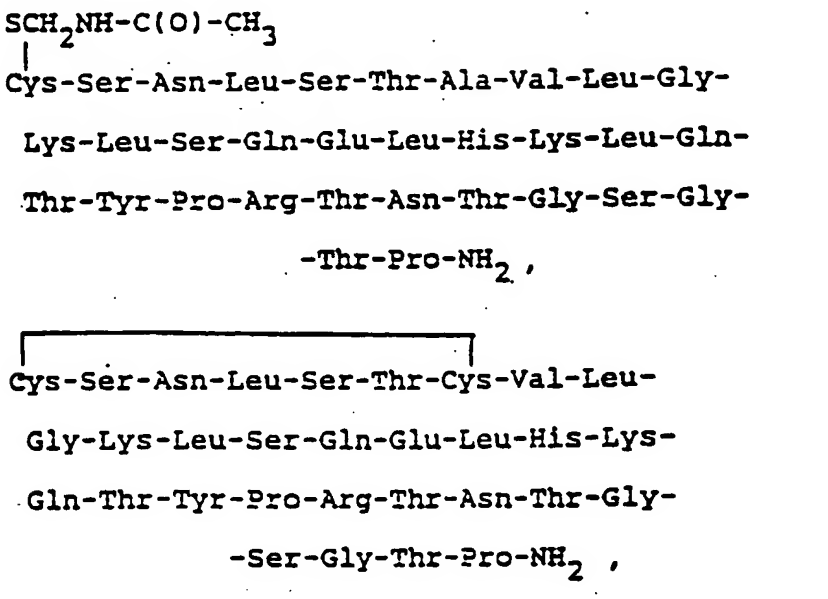
où :

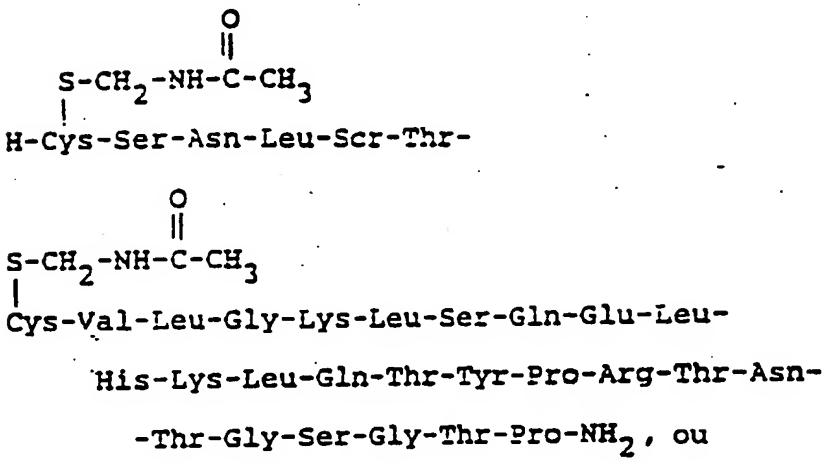
- R_1 représente S-n-alkyle, Cys ou H ; et

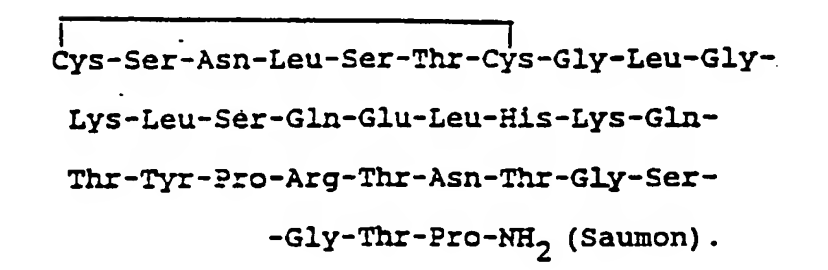
- R_2 représente S-n-alkyle ou H,

R_1 représentant S-n-alkyle, Cys ou H lorsque R_2 représente H, et R_2 représentant S-n-alkyle ou H lorsque R_1 représente H.

12. Composition intranasale selon l'une des revendications 1 ou 2, dans laquelle ledit polypeptide est :







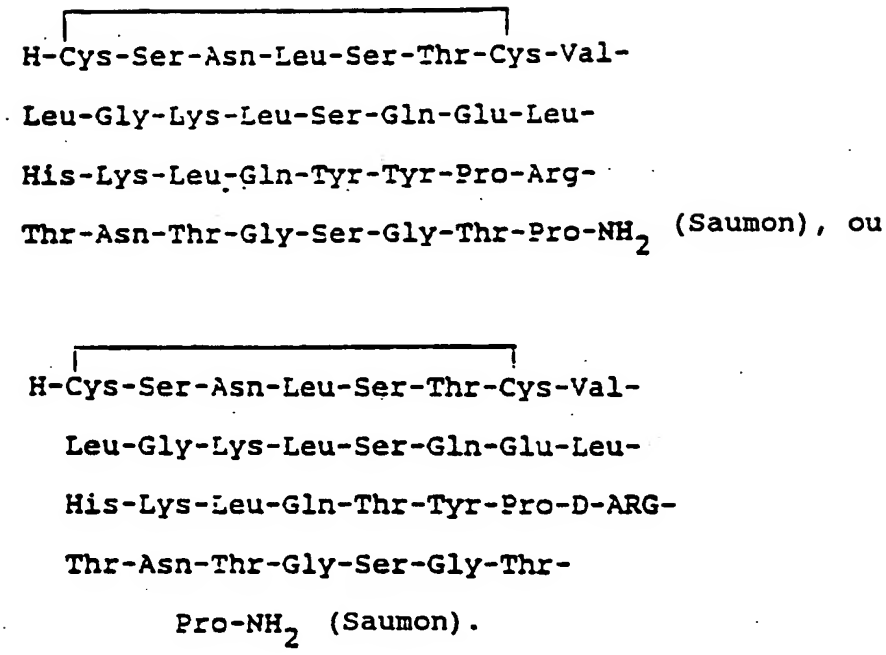
13. Composition intranasale selon l'une des revendications 1 ou 2, dans laquelle ledit polypeptide est :

Cys-Ser-Asn-Leu-Ser-Thr-Cys-Val-Leu-Gly-
Lys-Leu-Ser-Gln-Glu-His-
Lys-Leu-Gln-Thr-Tyr-Pro-Arg-
Thr-Asn-Thr-Gly-Ser-Gly-Thr-
-Pro-NH_2 (Saumon),

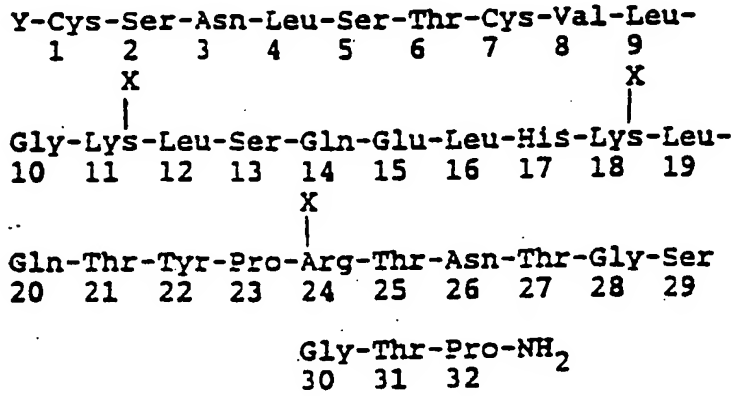
H-Cys-Ser-Asn-Leu-Ser-Thr-Cys-Val-Leu-Gly-
Lys-Leu-Ser-Gln-Glu-Leu-His-Lys-Leu-Gln-Thr-
Leu-Pro-Arg-Thr-Asn-Thr-Gly-Ser-Gly-Thr-Pro-
NH_2 (Saumon),

H-Cys-Ser-Asn-Leu-Ser-Thr-Cys-Gly-Leu-Gly-Lys-
Leu-Ser-Gln-Glu-Leu-His-Lys-Leu-Gln-Thr-Tyr-
Pro-Arg-Thr-Asn-Thr-Gly-Ser-Gly-Thr-Pro-NH_2 ,

H-Cys-Ser-Asn-Leu-Ser-Thr-Cys-Gly-
Leu-Gly-Lys-Leu-Ser-Gln-
Glu-Leu-His-Lys-Leu-Gln-Thr-
Tyr-Pro-D-ARG-Thr-Asn-Thr-Gly-
Ser-Gly-Thr-Pro-NH_2 (Saumon),



14. Composition intranasale selon l'une des revendications 1 ou 2, dans laquelle ledit polypeptide est :



où :

- Y représente N(a) décanoyle ; et
- X représente N(e) décanoyle.

15. Composition intranasale selon l'une des revendications 1 ou 2, dans laquelle ledit polypeptide est :

H_2N-Ala-Ser-Asn-Leu-Ser-Thr-Ala-Gly-Leu-Gly-
1 5 10

Lys-Leu-Ser-Gln-Glu-Leu-His-Lys-Gln-Thr-Tyr-
15 20

Pro-Arg-Thr-Asn-Thr-Gly-Ser-Gly-Thr-
25 30

Pro-(C=O)-NH_2.

16. Composition intranasale selon l'une des revendications 1 ou 2, dans laquelle ledit polypeptide est :

CH_3-CH_2-(C=O)-Hn-

Ala-Ser-Asn-Leu-Ser-Thr-Ala-Val-Leu-Gly-
1 5 10

Lys-Leu-Ser-Gln-Glu-Leu-His-Lys-Gln-Thr-Tyr-
15 20

Pro-Arg-Thr-Asn-Thr-Gly-Ser-Gly-Thr-Pro-
25 30

(C=O)-NH_2.

17. Procédé pour rehausser la biodisponibilité d'un polypeptide ayant une activité de calcitonine comprenant: l'addition de 0,0005% p/v à 10% p/v d'acide Δ-aminolévulinique à une composition comprenant 0,0001% p/v à 15% p/v d'un polypeptide ayant une activité de calcitonine et un excipient pharmaceutiquement acceptable.

18. Utilisation de l'acide Δ-aminolévulinique pour préparer une composition intranasale contenant de 0,0001% p/v à 15% p/v d'un polypeptide ayant une activité de calcitonine; de 0,0005% p/v à 10% p/v d'acide Δ-aminolévulinique ; et un excipient pharmaceutiquement acceptable.

19. Utilisation de l'acide Δ-aminolévulinique pour préparer une composition intranasale pour le traitement de l'hyperparathyroïdie, l'hypercalcémie idiopathique du petit enfant, la maladie de Paget, l'intoxication par la vitamine D ou les métastases osseuses ostéolytiques, lesdites maladies étant caractérisées par une hypercalcémie et des concentrations élevées en phosphate dans le sang, la composition intranasale étant définie à l'une quelconque des revendications 1 à 16.